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The Western Journal of Medicine

VOLUME 162 • NUMBER 1 JANUARY 1995

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Vaughn A. Starnes, M.D., *is Professor of Surgery at the University of Southern California School of Medicine, Chief of the Division of Cardiothoracic Surgery and Director of the USC Cardiothoracic Center at USC University Hospital, Childrens Hospital Los Angeles and Los Angeles County+USC Medical Center. Dr. Starnes earned his bachelor's degree in chemistry and medical degree at the University of North Carolina, Chapel Hill. He completed his general surgery training at Vanderbilt University, and then joined Stanford University, where he completed two years as a resident in cardiovascular surgery and one year as chief resident in cardiac transplantation. He joined USC in 1992.*

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New Drugs Update: A Clinician's Perspective
March 31-April 2, 1995 • Biloxi, MS

Rehab & Primary Care: Helping People Help Themselves
April 21-23, 1995 • Birmingham, AL

National Interactive Video Conference - The Brain At Risk: Preventing, Diagnosing & Managing Stroke
May 2, 1995

Musculoskeletal Impairment & Disability Evaluation
May 12-14, 1995 • New Orleans, LA

Geriatric Medicine: An Update on Diagnosis & Management
June 8-10, 1995 • San Antonio, TX

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The following programs contain in-depth information in a particular specialty, but may also be appropriate for primary care or allied health care professionals.

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March 9-12, 1995 • Atlanta, GA

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Target Audience: Radiologists
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The Shoulder Symposium
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April 7-8, 1995 • Pine Mountain, GA

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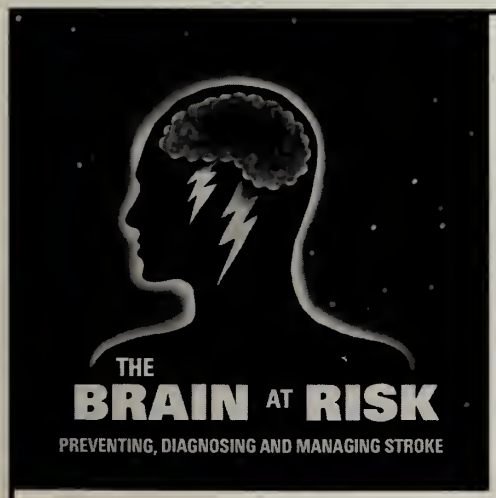

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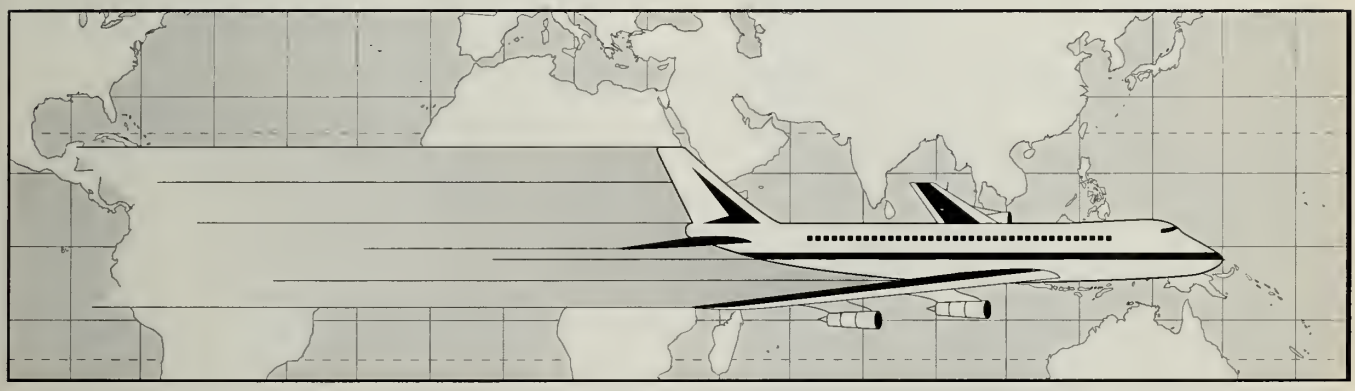

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ABSTRACTS JANUARY 1995

(Friedman BM: Early interventions in the management of acute uncomplicated myocardial infarction. West J Med 1995; 162:19-27)

The demonstration that the vast majority of acute transmural myocardial infarctions are caused by an occlusive thrombus in the coronary artery, together with the concept that myocardium can be salvaged for a period of time after the onset of such occlusion, has heralded a new era of management of this disorder. This involves an aggressive interventional approach aimed at restoring coronary artery patency early while decreasing myocardial oxygen demands. Abundant data show that coronary flow can be reestablished using either intravenous chemical thrombolytic agents (tissue-type plasminogen activator and streptokinase), percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Conjunctive aspirin or heparin therapy (or both) is effective in maintaining vessel patency once perfusion is restored. Myocardial oxygen demand can be reduced, where feasible, by pharmacotherapy and control of the patient's associated pain and anxiety. The b-adrenergic blockers and nitrates are particularly suitable in this regard, and angiotensin-converting enzyme inhibitors favorably affect infarct expansion and ventricular remodeling. With such an approach, infarct size can be reduced, leading to improved left ventricular function—the prime determinant of morbidity and mortality in patients with acute infarction. The in-hospital mortality has fallen from about 30% three decades ago to less than 8% in many coronary care units.

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MYOCARDIAL INFARCTION

(Friedman BM: Early interventions in the management of acute uncomplicated myocardial infarction. West J Med 1995; 162:19-27)

The demonstration that the vast majority of acute transmural myocardial infarctions are caused by an occlusive thrombus in the coronary artery, together with the concept that myocardium can be salvaged for a period of time after the onset of such occlusion, has heralded a new era of management of this disorder. This involves an aggressive interventional approach aimed at restoring coronary artery patency early while decreasing myocardial oxygen demands. Abundant data show that coronary flow can be reestablished using either intravenous chemical thrombolytic agents (tissue-type plasminogen activator and streptokinase), percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Conjunctive aspirin or heparin therapy (or both) is effective in maintaining vessel patency once perfusion is restored. Myocardial oxygen demand can be reduced, where feasible, by pharmacotherapy and control of the patient's associated pain and anxiety. The b-adrenergic blockers and nitrates are particularly suitable in this regard, and angiotensin-converting enzyme inhibitors favorably affect infarct expansion and ventricular remodeling. With such an approach, infarct size can be reduced, leading to improved left ventricular function—the prime determinant of morbidity and mortality in patients with acute infarction. The in-hospital mortality has fallen from about 30% three decades ago to less than 8% in many coronary care units.

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MYOCARDIAL INFARCTION

(Friedman BM: Early interventions in the management of acute uncomplicated myocardial infarction. West J Med 1995; 162:19-27)

The demonstration that the vast majority of acute transmural myocardial infarctions are caused by an occlusive thrombus in the coronary artery, together with the concept that myocardium can be salvaged for a period of time after the onset of such occlusion, has heralded a new era of management of this disorder. This involves an aggressive interventional approach aimed at restoring coronary artery patency early while decreasing myocardial oxygen demands. Abundant data show that coronary flow can be reestablished using either intravenous chemical thrombolytic agents (tissue-type plasminogen activator and streptokinase), percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Conjunctive aspirin or heparin therapy (or both) is effective in maintaining vessel patency once perfusion is restored. Myocardial oxygen demand can be reduced, where feasible, by pharmacotherapy and control of the patient's associated pain and anxiety. The b-adrenergic blockers and nitrates are particularly suitable in this regard, and angiotensin-converting enzyme inhibitors favorably affect infarct expansion and ventricular remodeling. With such an approach, infarct size can be reduced, leading to improved left ventricular function—the prime determinant of morbidity and mortality in patients with acute infarction. The in-hospital mortality has fallen from about 30% three decades ago to less than 8% in many coronary care units.

CORONARY THROMBOSIS
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References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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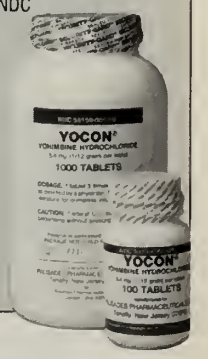

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

January 25-27—**Clinical Recognition and Management of Heart Disease.** American College of Physicians and Univ of Arizona College of Medicine at University Medical Center, Tucson. Wed-Fri. Contact: (215) 351-2400, ext 2600.

February 6-10—**Psychopharmacology Review Course.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Mon-Fri. Contact: Lynne Mascarella, U of A.

February 12-16—**International Congress VIII on Endovascular Interventions: Breaking the Barriers.** American College of Angiology at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: (602) 266-2200.

February 16-18—**Mayo Interactive Surgical Symposium.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Conference Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 16-18—**18th Annual Midwinter Symposium—Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix Ob/Gyn Society at Scottsdale Plaza Resort. Thurs-Sat. Contact: Beverlee Anderson, (602) 267-5366.

February 17-19—**21st Annual Scientific Meeting—Anesthesia for the 90s.** University of Arizona College of Medicine and Arizona Society of Anesthesiologists at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. (602) 947-5400.

February 20-23—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: Lynne Mascarella, U of A.

February 23-24—**Hepatology Update 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 23-25—**21st Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: (602) 274-7479.

February 24-25—**Mayo Plastic Surgery Symposium.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital at Marriott's Camelback Inn, Scottsdale. Mon-Thurs. Contact: (602) 239-5783.

March 5-9—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at Marriott's Camelback Inn Resort, Scottsdale. Sun-Thurs. Contact: Lynne Mascarella, U of A.

March 8-10—**Clinical Reviews 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Wed-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Frequently Encountered GYN Problems in Primary Care.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Controversies in Hypertension.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 17-19—19th **Annual James H. McDonald Urological Seminar.** Maricopa Medical Center and Phoenix Urologic Society at Scottsdale Plaza Resort. Fri-Sun. Contact: Beverlee Anderson, (602) 267-5366.

March 25-30—**Skeletal Radiology.** Allegheny General Hospital and Medical College of Pennsylvania at the Arizona Biltmore, Phoenix. Sat-Thurs. Contact: (412) 359-4952.

March 30-April 1—**4th Annual Urogynecology and Disorders of the Pelvic Floor.** Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30-April 2—**Mammography in March: Breast Diseases and Imaging.** Maricopa Medical Center at Marriott Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

May 6-9—**2nd Mayo Telemedicine Symposium and 2nd International Symposium on the Medical Aspects of Telemedicine.** Mayo Foundation. Sat-Tues. Contact: (800) 323-2688.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 15-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Resort at Kaanapali Beach, Maui, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

May 18-21—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $350. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691

February 3-5—**33rd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, MD, Director, PO Box 54700, Los Angeles 90054. (213) 669-2262.

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St. Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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NEWPORT BEACH, CALIFORNIA

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4th Annual Internal Medicine Board Review Course
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LE MERIDIEN HOTEL
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(Continued from Page 13)

CARDIOLOGY

April 28-30—**Arrhythmias: Interpretation, Diagnosis and Management**. Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

May 11-13—**5th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

January 31-February 4—**Critical Care by Design.** Society of Critical Care Medicine at Moscone Center, San Francisco. Tues-Sat. 30.5 hrs. $600. Contact: SCCM, 8101 E Kaiser Blvd, Anaheim 92808-2259. (714) 282-6000.

March 13-17—**Critical Care Medicine.** USC at Caesars Palace, Las Vegas. Mon-Fri. 33 hrs. $595-$720. Contact: USC

DERMATOLOGY

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 24-29—**California Trauma Conference.** UCSD at Hyatt Regency, San Diego. Tues-Sun 20 hrs. $395.Contact: UCSD.

February 19-24—**18th Annual Emergency Medicine: 1995.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD

March 6-10—**15th Annual Mammoth Mountain Emergency Medicine Ski Conference**. American College of Emergency Physicians at Mammoth Lakes. Mon-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 650-4156.

March 13-17—**Emergency Medicine Symposium**. UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 16-17—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at San Francisco. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St. Ste A, Ashland, OR 97520. (800) 452-7475.

June 20-21—**High Risk Emergency Medicine and Acute Care**. American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St. Ste A, Ashland, OR 97520. (800) 452-7475.

EPIDEMIOLOGY/INFECTIOUS DISEASE

January 25-27—**Epidemiology and Prevention of Infectious Disease**. UCSF at Ritz-Carlton, San Francisco. Wed-Fri. 14.5 hrs; $395. Contact: UCSF.

February 3-4—**13th Annual Infectious Disease Conference.** UCD at Hilton Hotel, Sacramento. Fri-Sat. 11 hrs. Contact: UCD.

April 2-4—**5th Annual Meeting of the Society for Healthcare: Epidemiology of America.** UCSD at Town & Country, San Diego. Sun-Tues. 17 hrs. $435. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

January 27-January 30—**47th Annual Scientific Assembly—California Academy of Family Physicians.** Hyatt Regency Embarcadero. Fri-Mon. 20 hrs. Contact: Clark Franklin, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104-3824. (415) 394-9121.

February 2-4—**Neurology for the Non-Neurologists.** UCSD at Doubletree Hotel, San Diego. Thurs-Sat. Contact: UCSD.

February 7-April 25—**Common Problems in Primary Care**. USC at Health Sciences Campus, Los Angeles. Tuesday Evenings. 36 hrs. $475. Contact: USC.

February 15-19—**The Practicing Physician's Approach to the Difficult Headache Patient.** Danemiller Memorial Educational Foundation at Marriott's Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. 21.25 hrs. Contact: DHC Research & Educational Foundation, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

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March 29-31—**Annual Review in Family Medicine**. UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

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(Continued on Page 82)

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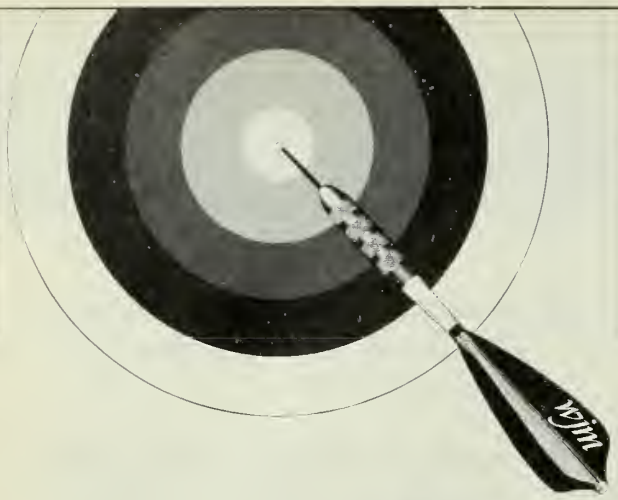

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In the battle against allergic rhinitis

A FIRST LINE OF DEFENSE

Symptomatic relief superior to QD non-sedating antihistamines[1,2]

See charts on reverse side

QD staying power

Convenient once-daily dosing for better compliance

Onset of action as early as 12 hours[3]

Maximum benefit is generally seen within 3 to 4 days[3]

Excellent safety profile

No measurable effect on HPA function at recommended doses[4,5]

The most commonly reported side effects are headache and nasal irritation

ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Please see brief summary of prescribing information on following page.

1 ONCE DAILY Nasacort® Nasal Inhaler
(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using
BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with vancella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m²/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m²/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m²/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m²/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m²/day or 110 mcg/m²/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m²/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m²/day and 7.0 mcg/m²/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m²/day in the rat and 320, 640 and 1280 mcg/m²/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m²/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included, dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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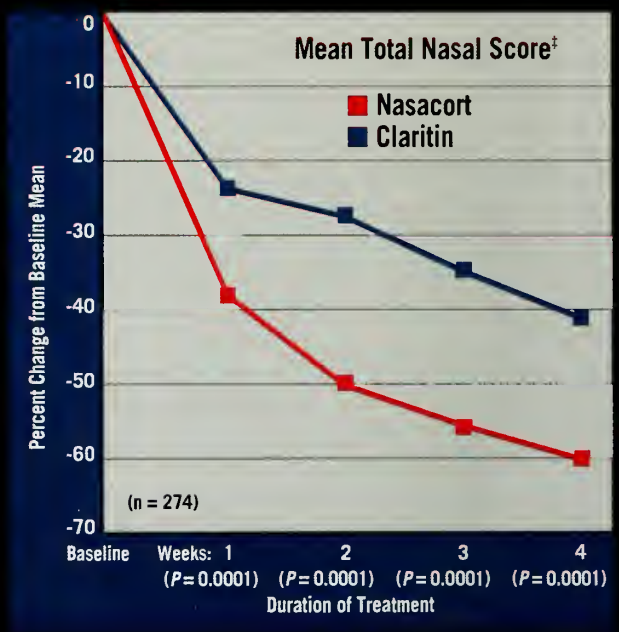
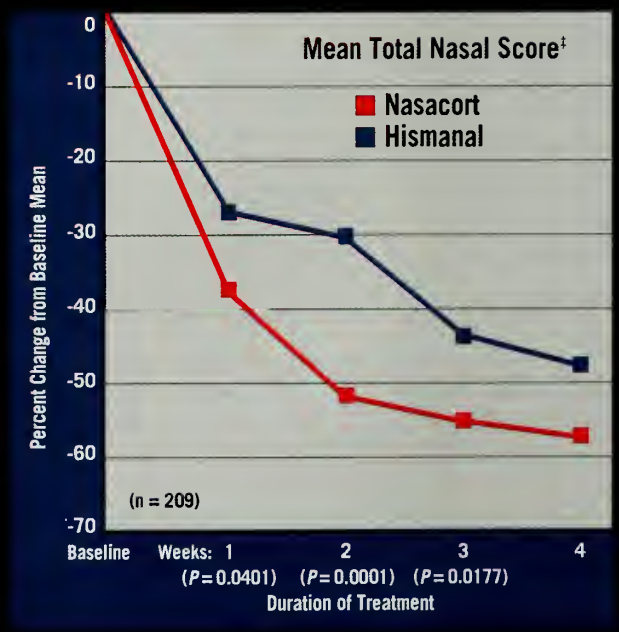
Superior symptomatic relief vs. QD non-sedating antihistamines[1,2]

NASACORT VS. CLARITIN[1,*]



‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[2,§]



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*

† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*

§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

REFERENCES

1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom O, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

Articles

Early Interventions in the Management of Acute Uncomplicated Myocardial Infarction

BRIAN M. FRIEDMAN, MD, *Kansas City, Kansas*

The demonstration that the vast majority of acute transmural myocardial infarctions are caused by an occlusive thrombus in the coronary artery, together with the concept that myocardium can be salvaged for a period of time after the onset of such occlusion, has heralded a new era of management of this disorder. This involves an aggressive interventional approach aimed at restoring coronary artery patency early while decreasing myocardial oxygen demands. Abundant data show that coronary flow can be reestablished using either intravenous chemical thrombolytic agents (tissue-type plasminogen activator and streptokinase), percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Conjunctive aspirin or heparin therapy (or both) is effective in maintaining vessel patency once perfusion is restored. Myocardial oxygen demand can be reduced, where feasible, by pharmacotherapy and control of the patient's associated pain and anxiety. The β-adrenergic blockers and nitrates are particularly suitable in this regard, and angiotensin-converting enzyme inhibitors favorably affect infarct expansion and ventricular remodeling. With such an approach, infarct size can be reduced, leading to improved left ventricular function—the prime determinant of morbidity and mortality in patients with acute infarction. The in-hospital mortality has fallen from about 30% three decades ago to less than 8% in many coronary care units.

(Friedman BM: Early interventions in the management of acute uncomplicated myocardial infarction. West J Med 1995; 162:19-27)

Despite a dramatic decline in the number of cardiovascular deaths during the past 30 years, atherosclerotic occlusive coronary artery disease and acute myocardial infarction (MI) remain the leading causes of death and cardiovascular morbidity in the United States, where an estimated 1.5 million people suffer an acute infarction each year.[1(p1)] Advances in the understanding of the pathogenesis of acute MI and the introduction of appropriate therapeutic interventions have resulted, in recent years, in a considerable decline in the in-hospital mortality rate.

The interventional era was heralded by pioneering angiographic work that found that 87% of patients with the clinical and electrocardiographic features of acute transmural MI have an occlusive thrombus, usually overlying a complicated atherosclerotic plaque, in an epicardial coronary artery or one of its major branches.[2] In the absence of an adequate collateral blood supply, myocyte necrosis in the zone supplied by the occluded vessel will ensue in 30 to 40 minutes. The resulting infarction spreads outward in a wave-front pattern, from the subendocardium to the epicardium, ultimately becoming transmural in distribution.[3] Experimental and clinical data suggest that myocardium is possibly salvageable for as long as six hours after coronary occlusion.[4] This period provides clinicians with a "window of opportunity" to apply interventions that might abort or retard infarct progression.

Survival following an acute MI is inversely related to infarct size, which in turn is dependent on an ongoing imbalance between myocardial oxygen supply and demand—that is, ischemia—after coronary artery occlusion. The sooner this ischemia can be reversed, the smaller will be the ensuing infarct, with a resultant improvement in both survival and quality of life.

Myocardial oxygen supply depends primarily on an intact coronary arterial supply, the ability of hemoglobin to deliver oxygen to the metabolizing tissues, and an adequate diastolic filling period. Myocardial oxygen demand, on the other hand, is determined by the heart rate, myocardial contractility, and ventricular wall tension. Both limbs of the supply-demand equation warrant attention in the treatment of patients with acute MI.

In Table 1 are listed interventions that may improve the supply component of the ischemia equation.

Improving Myocardial Oxygen Supply

Oxygen

Moderate hypoxemia may accompany acute MI even in the absence of left ventricular failure and pulmonary

From the Department of Internal Medicine, Section of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City.
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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
GISSI-2 (-3) = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 2 (3)
ISIS-1 (-2, -3, -4) = First (Second, Third, Fourth) International Study of Infarct Survival
MI = myocardial infarction
NS = not significant
PTCA = percutaneous transluminal coronary angioplasty
tPA = tissue-type plasminogen activator

edema. This is thought to be mediated by a ventilation-perfusion mismatch.[5] Patients with moderate hypoxemia should receive supplemental oxygen through a face mask or nasal cannulae. The benefits in terms of increasing the myocardial oxygen supply tend to override the possibly deleterious effect of increasing systemic vascular resistance and myocardial oxygen demand.

Chemical Thrombolysis

The survival advantage of the three major thrombolytic agents used in patients with an acute MI (tissue-type plasminogen activator [tPA], streptokinase, and anisoylated plasminogen streptokinase activator complex) has been confirmed in five large, randomized, placebo-controlled trials.[6,7] The pooled data from these studies revealed about a 27% reduction in mortality when the agents were administered early after the onset of MI, as determined by symptoms.[6] Despite this convincing benefit, fewer than 15% of patients with acute MI who are admitted to hospital in the United States receive intravenous thrombolytic therapy.[7] The reasons for the low use rate include ignorance, apathy, and fear—often unfounded—of catastrophic side effects, as well as a number of ongoing controversial issues pertaining to intravenous thrombolysis. These relate to the choice of agent, absolute and relative contraindications, the duration of the window of opportunity, and the optimal conjunctive therapy.

Intravenous tPA is more efficient at restoring vessel patency of occluded infarct vessels than is streptokinase, as evidenced by superior 90-minute patency rates (76% versus 51%).[8] If the premise that "time is muscle" is correct, then earlier vessel patency should translate into increased myocardial salvage, superior left ventricular function, and improved survival. Two megatrials, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 2 (GISSI-2) and the Third International Study of Infarct Survival (ISIS-3), in which more than 60,000 patients were collectively and randomly selected, convincingly showed no benefit in terms of survival following treatment with either intravenous streptokinase or tPA.[9,10] The discordant results between the survival rates in these trials and earlier angiographic patency data possibly relate to the way in which conjunctive heparin therapy was used. In both trials this therapy was administered subcutaneously and was delayed. Thus, any possible benefit from tPA in terms of early patency may have been lost because of rethrombosis and reocclusion as a consequence of inadequate anticoagulation during the critical postlytic period.

TABLE 1.—*Interventions That Potentially Improve Myocardial Oxygen Supply*

Provide supplemental oxygen
Restore vessel patency
Chemical thrombolysis
Percutaneous transluminal coronary angioplasty
Coronary artery bypass grafting
Maintain vessel patency
Aspirin
Heparin
Alleviate coronary spasm
Improve collateral blood supply

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial randomly assigned more than 41,000 patients with acute MI to four treatment arms: "front-loaded" tPA and the immediate administration of intravenous heparin; streptokinase and the immediate administration of intravenous heparin; streptokinase and a delayed administration of subcutaneous heparin; and combined use of tPA and streptokinase (Table 2). The 30-day mortality data revealed that the accelerated-tPA regimen afforded a significant survival advantage over both streptokinase-treated groups (6.3% versus 7.3%; P = .001).[11] In practical terms, the 14% survival advantage translates into a saving of 10 lives per 1,000 patients treated with tPA compared with those given streptokinase. This benefit was seen in patients with both anterior- and inferior-wall infarct locations, but was more pronounced in those with anterior wall infarcts.

In an angiographic substudy, 80.8% of infarcted vessels were patent, with good flow, in tPA-treated patients, compared with 58.3% in the streptokinase-treated groups (P = .001).[12] This confirms previous angiographic data and tends to support the theory that restoring flow earlier is associated with improved myocardial salvage and survival.

Although the more aggressive tPA therapy was associated with substantially more hemorrhagic strokes than therapy with streptokinase (Table 2), the combined end point of disabling stroke and death remained significantly lower (6.9% versus 7.8%; P = .006). Elderly patients (older than 75 years) had a greater risk of stroke—hemorrhagic and nonhemorrhagic—and showed less benefit of reduced mortality from tPA therapy than their younger counterparts. These data may support the use of a less aggressive intravenous lytic strategy—streptokinase and subcutaneous heparin—in an elderly patient with an inferior wall infarct.

Accumulating data suggest that thrombolytic agents administered beyond the six-hour period may be beneficial. This was initially recognized in the Second International Study of Infarct Survival (ISIS-2) trial in

TABLE 2.—*Major Clinical and Angiographic Outcomes in the GUSTO Trial**

Treatment Group	Patients, %			
	Mortality (30 days)	Patency (90 min)	Stroke (Hemorrhagic)	Stroke (Total)
Streptokinase plus heparin (SQ)	7.2	55.6	0.49	1.22
Streptokinase plus heparin (IV)	7.4	61	0.54	1.40
tPA plus heparin (IV)	6.3	80.8	0.72	1.55
tPA and streptokinase	7.0	73.1	0.94	1.64
P value†	.001	.03	.09	.31

GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, IV = intravenous, SQ = subcutaneous, tPA = tissue-type plasminogen activator

*From the GUSTO investigators.[11]
†tPA versus streptokinase.

which patients who were randomly selected from 7 to 24 hours following an acute MI had a 22% survival advantage over controls at 5 weeks.[13] The Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur (EMERAS) trial, which specifically addressed late thrombolysis, revealed a trend toward improved survival in patients treated from 7 to 12 hours after the start of symptoms.[14] Pooled data from three late-entry trials revealed a significant reduction in mortality from 13.1% to 11.1% ($P < .001$) in patients receiving thrombolytic therapy between 6 and 24 hours after chest pain onset.[7] In such patients the period of viability may be prolonged by intermittent coronary artery occlusion and reopening, as thrombosis and endogenous thrombolysis compete, or by an adequate collateral blood supply. In addition, there may be advantages to vessel patency independent of myocardial salvage, such as improved healing, prevention or amelioration of infarct expansion, and electrical stability. The late administration of thrombolytic agents is justified if there is evidence of a stuttering evolution of infarction, such as ongoing chest pain or persistent ST-segment elevation on an electrocardiogram.

Finally, although thrombolytic agents have consistently been shown to modify the natural history of acute MI, their use is associated with a number of problems and side effects. These include major and minor hemorrhage, reperfusion arrhythmias, stroke, cardiac rupture, reocclusion, and, in the case of streptokinase, allergic reactions. Nonetheless, the possible benefits far outweigh the risks, and all eligible patients with an acute MI who do not have a contraindication to thrombolytic agents (Table 3) and who still have features of ongoing infarction at the time of presentation should receive such an agent.

Conjunctive Therapy

Conjunctive therapy refers to treatment that is designed to potentiate thrombolysis by accelerating or augmenting the extent of clot dissolution, preventing or retarding reocclusion, or both. Thrombolysis can paradoxically initiate the activation of platelets and the coagulation cascade.[15] Thus, the efficacy of coronary thrombolysis depends not only on the intensity and persistence of fibrinolysis per se, but also on inhibition of the prothrombotic phenomena. At this time, two conjunctive agents, heparin and aspirin, have been extensively evaluated in the treatment of acute MI.

Heparin. Heparin inhibits the thrombotic cascade by potentiating antithrombin III, by a direct antithrombin effect, and by interfering with platelet function. The major benefit of heparin use in patients receiving lytic therapy relates to a reduction in the incidence of reocclusion by inactivating free thrombin released in the vicinity of the thrombi undergoing lysis. Heparin confers additional advantage by preventing the occurrence of deep venous thrombosis, pulmonary embolism, and mural thrombosis. Early (90-minute) angiographic studies failed to show improved vessel patency when heparin was administered conjunctively with tPA.[16] Three later postthrombolytic trials, in which angiography was deferred for 18, 40, and 80 hours, respectively, revealed substantial improvement in infarcted vessel patency in those patients randomly assigned to receive heparin.[17-19] These data suggest that early patency is determined largely by the efficacy of the lytic agent, whereas sustained patency depends on efficient conjunctive therapy. Based on the available data, particularly when tPA is the agent used to achieve lysis, a concomitant bolus of intravenous heparin (5,000 units) should be administered. This should be followed by a continuous infusion titrated to maintain the activated partial thromboplastin time at two to two and a half times control.

Aspirin. The pharmacologic action of aspirin is mediated by the inhibition of cyclooxygenase, the enzyme responsible for the formation of thromboxane A_2, a potent mediator of platelet activation and vasoconstriction. In the ISIS-2 trial, patients were randomly assigned to receive 160 mg on the day of infarction and daily thereafter for four weeks.[13] Such therapy was associated with a 23% ($P < .0001$) reduction in mortality compared with placebo. When aspirin was combined with streptokinase, the effect seemed to be additive, with a 43% reduction in mortality compared with control. Furthermore, aspirin substantially reduced the risk of reinfarction and nonfatal stroke by 44% and 46%, respectively. When different dosage schedules have been evaluated, the higher dosages were associated with increased side effects without demonstra-

TABLE 3.—*Contraindications to Thrombolytic Therapy*

Absolute
Active internal hemorrhage
Long-term oral anticoagulant use
Intracranial neoplasia, aneurysm, or arteriovenous malformation
Bleeding diathesis
Recent trauma or intracranial or intraspinal surgery (within 2 mo)
Major operation (within 2 wk)
Pregnancy
Severe hypertension (systolic blood pressure [BP] > 180 mm of mercury, diastolic BP > 110 mm of mercury)
Allergy to streptokinase or previous exposure
Relative
Acute pericarditis
Bacterial endocarditis
Hemostatic defects due to severe renal or hepatic disease
High likelihood of left atrial or ventricular thrombus
Prolonged cardiopulmonary resuscitation
Diabetic hemorrhagic retinopathy
Menstruation

ble additional therapeutic benefit.[20] The current suggested dose in the United States is 325 mg initially and daily thereafter.

Percutaneous Transluminal Coronary Angioplasty

Following successful clot lysis, the precipitating complicated atherosclerotic plaque persists, with the propensity to cause rethrombosis, reocclusion, and reinfarction. Therefore, a number of strategies using percutaneous transluminal coronary angioplasty (PTCA) have evolved so as to address not only the offending thrombus but the underlying plaque as well.

Direct PTCA. Two groups working independently showed that direct PTCA—angioplasty without antecedent thrombolysis—can be performed safely and with a greater than 97% success rate in centers with experience in this technique.[21,22] In the Primary Angioplasty in Myocardial Infarction trial, the in-hospital mortality in the PTCA- and tPA-treated groups was 6.5% and 2.6%, respectively ($P = .06$). The difference reached statistical significance when patients "not at low risk" were analyzed. Patients undergoing direct PTCA had fewer intracranial hemorrhages, fewer incidents of reinfarction, less postinfarction angina, and higher infarct artery patency rates than their counterparts who received thrombolytic therapy. A caveat of these excellent results is that they probably apply to a few centers with highly skilled operators. In addition, widespread use of this technique is limited by the fact that fewer than 18% of hospitals in the United States have catheterization facilities for angioplasty.[23] Nevertheless, in institutions with catheterization capabilities, direct PTCA is a useful alternative in patients with contraindications to thrombolysis. It remains the treatment of choice for managing patients with acute MI complicated by cardiogenic shock. A meta-analysis was done to examine the use of direct PTCA in this subgroup, and a cumulative mortality rate of 44% was reported—approximately half the rate in patients treated with thrombolytic agents.[24]

Immediate PTCA. The administration of routine immediate PTCA has been compared with doing delayed angioplasty in three large, well-controlled trials: the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial, the European Cooperative study, and phase IIA of the Thrombolysis in Myocardial Infarction (TIMI IIA) trial.[26-28] In all three trials, patients treated with thrombolysis were randomly assigned to undergo immediate angioplasty or deferred, elective angioplasty at times varying from 18 to 48 hours to 7 to 10 days after initial lytic therapy. All three trials showed immediate angioplasty to be more hazardous and associated with an increased incidence of reocclusion, reinfarction, and the need for coronary artery bypass grafting. The groups receiving angioplasty also had considerably more hemorrhage, hypotension, and a trend toward increased mortality.

Deferred or delayed PTCA. Two large, randomized, controlled trials have assessed the efficacy of routine angioplasty 18 to 48 hours after thrombolytic therapy and compared this with a conservative strategy in which this technique was reserved for those patients with spontaneous or exercise-induced ischemia.[28,29] In both, the more aggressive approach was associated with a higher complication rate with no improvement in left ventricular function or survival. It therefore seems prudent to adopt a policy of "watchful waiting" for patients who appear to be clinically stable following thrombolysis and to reserve using PTCA for those with postinfarction angina or demonstrable reversible ischemia on noninvasive testing.

Surgical Intervention

Urgent coronary artery bypass grafting in evolving acute MI has a number of advantages over other methods of reperfusion. The revascularization can be more complete when multivessel disease is present, reperfusion injury may be limited by the administration of intraoperative perfusate, the high rate of graft patency affords a predictable conduit, and patients are less likely to suffer from postinfarction angina.[30] With experience, this approach is feasible, safe, and can be undertaken with acceptably low mortality rates. In a nonrandomized series of patients operated on during infarct evolution, an overall operative mortality of 4.4% was reported among 701 patients who underwent coronary artery bypass grafting as their primary treatment of acute MI within 24 hours of the start of symptoms.[31] The mortality rate of the 440 patients in the group with transmural infarction was 1.3% per year during the ensuing ten years of follow-up. In a small randomized trial involving 68 patients, the use of urgent coronary artery bypass grafting was compared with that of conventional medical therapy (without thrombolytics) in patients presenting within four hours of the beginning of symptoms. The in-hospital mortality was 2.9% in the

TABLE 4.—*Interventions That Potentially Decrease Myocardial Oxygen Demand*

Pain relief
β-Adrenergic blockers
Angiotensin-converting enzyme inhibitors
Nitrates
Calcium channel blockers

surgically treated group and 8.8% in the medically treated group (P = not significant [NS]).[32] Because the medically treated group did not receive thrombolytics, no inference can be made about the relative merits of these different reperfusion techniques. Nevertheless, these data further demonstrate the efficacy of surgical revascularization as an alternative strategy when the skills are available.

Because of a lack of general availability and the enormous costs involved, surgical intervention is unlikely to become part of the routine early management of uncomplicated acute MI. It should thus be reserved for specific patient subsets, including those with cardiogenic shock and anatomy unsuitable for PTCA, postinfarction angina and left main-stem or triple-vessel disease, failed PTCA associated with ongoing hemodynamic instability, or mechanical complications.[33]

Decreasing Myocardial Oxygen Demand

A variety of pharmacologic agents have hemodynamic properties that potentially decrease myocardial oxygen demand (Table 4). Effective treatment of pain and anxiety will also favorably affect this component of ischemia. Persistent pain generally indicates ongoing ischemia of possibly viable myocardium. Therefore, analgesia should be administered concomitantly with those measures that might reverse such ischemia. Morphine sulfate remains the cornerstone of pain relief and also serves to allay some of the anxiety accompanying acute MI. Morphine has additional hemodynamic advantages by blocking sympathetic efferent discharge in the central nervous system, resulting in venous and arterial vasodilation and consequent reductions in both preload and afterload.[34]

β-Adrenergic Receptor Blockers

β-Adrenergic receptor blockers reduce heart rate, myocardial contractility, and left ventricular wall tension, and thus they have a favorable effect on all three major determinants of myocardial oxygen demand. They also improve myocardial blood supply by prolonging the diastolic filling period and diverting blood toward the subendocardium. Additional advantages in patients with acute MI may be conferred by their powerful antiarrhythmic potential and an effect on myocardial metabolism resulting in more efficient energy use.[35] In the ISIS-1 trial, 16,027 patients with suspected acute infarction were randomly selected to receive intravenous atenolol at diagnosis, followed by oral therapy if adverse effects did not occur.[36] There was a 15% reduction in vascular mortality at seven days in the group receiving β-blockers compared with controls ($P < .04$). In the Metoprolol in Acute Myocardial Infarction (MIAMI) trial, the 13% mortality reduction observed at 14 days in patients treated with intravenous and subsequent oral metoprolol did not reach statistical significance. Subgroup analysis, however, revealed that those patients considered to be at high risk had a 29% survival advantage ($P = .033$).[37]

A meta-analysis of the 31 randomized trials using early β-blockade in patients with acute MI revealed a 13% reduction (±6%; $P < .02$) in the odds of death.[35] Most of the benefit occurred in the first 48 hours of therapy, suggesting a reduction in the incidence of ventricular fibrillation and myocardial rupture. When all major fatal and nonfatal events—death, nonfatal cardiac arrest, and nonfatal reinfarction—were compared, a 16% reduction by β-blockade was calculated ($P < .0001$).

The conjoint use of β-blockers and thrombolytic therapy has been assessed in only one major trial, the phase IIB of the Thrombolysis in Myocardial Infarction (TIMI IIB) trial.[28] This study was designed primarily to assess the role of prophylactic, deferred PTCA after thrombolysis. In the β-blocker component of the trial, eligible patients were randomly assigned to receive either immediate intravenous, followed by oral, metoprolol tartrate or deferred oral metoprolol tartrate six days after lytic therapy. The rates of nonfatal reinfarction and recurrent ischemia at six weeks were reduced by 49% ($P = .02$) and 27% ($P = .0005$), respectively, in the immediate-therapy group. A survival advantage could not be shown in the small number of patients studied.

β-Blockade is generally avoided when a patient has one or more of the following: hypotension (systolic blood pressure <100 mm of mercury), bradycardia (rate <60 beats per minute), severe left ventricular failure, cardiogenic shock, and heart block (PR interval >240 milliseconds, second- or third-degree atrioventricular block).

Angiotensin-Converting Enzyme Inhibitors

The angiotensin-converting enzyme (ACE) inhibitors block the production of angiotensin II, the biologically active octapeptide, which augments the contraction of vascular smooth muscle and promotes the renal retention of sodium. The inhibition of converting enzyme further enhances vasodilation by increasing the levels of bradykinin and facilitating the formation of other prostaglandin vasodilators and endothelial-derived relaxing factor.[38] Studies of animals and clinical studies have suggested that these agents attenuate the ventricular remodeling, infarct expansion, and aneurysm formation in the early postinfarction period.[39,40] Additional benefits may be conferred by their antiarrhythmic and free-radical scavenging effects.

Recent data from the megatrials support the early use of ACE inhibitors after acute MI (Table 5).[41-43] In the GISSI-3 trial,[41,42] the use of lisinopril was associated with a substantial reduction in the six-week mortality compared with that of placebo (6.3% versus 7.1%), whereas the use of early captopril in the ISIS-4 study[43] had a favorable effect on the 35-day mortality (6.9% versus 7.3%),

TABLE 5.—*Effects of Angiotensin-Converting Enzyme Inhibitors and Magnesium on Mortality in Patients With Acute Myocardial Infarction**

Drug Treatment (Study)	Patients, % Treated	Patients, % Control
Captopril (ISIS-4)†	6.9	7.3‡
Lisinopril (GISSI-3)§	6.3	7.1‖
Magnesium (ISIS-4)†	7.3	6.9¶

GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3, ISIS-4 = Fourth International Study of Infarct Survival

*From the GISSI-3 Research Group,[40] Ferguson,[41] and the ISIS-4 Collaborative Group.[42]
†Percentages are based on a 35-day mortality. ‡$P = .04$.
§Percentages are based on a 6-week mortality. ‖Odds ratio = 0.88.
¶P = not significant.

despite a higher incidence of hypotension. This benefit appeared to be most pronounced in patients at highest risk—those with congestive heart failure, a history of previous myocardial infarction, and an anterior location of the infarct. These data complement those of the Survival and Ventricular Enlargement (SAVE) trial that showed a significant survival advantage for the use of captopril when started 3 to 16 days after an anterior-wall MI with left ventricular dysfunction (ejection fraction < 0.4%).[44] Treatment was associated with a 19% ($P = .02$) reduction in total mortality at 3.6 years and a substantial decrease in the incidence of heart failure and the rate of recurrent myocardial infarction.

Nitrates

The organic nitrates are prodrugs that, after conversion to nitric oxide, activate guanylate cyclase, causing a cascade of events that result in the relaxation of vascular smooth muscle. The hemodynamic effects of these agents render them suitable for treating all aspects of coronary artery disease, including acute MI. Venodilation and arterial vasodilation, by reducing both preload and afterload, diminish the myocardial oxygen ventilation rate. These agents also alleviate coronary artery spasm, increase flow in collateral vessels, and divert blood from the subepicardium toward the more vulnerable subendocardium. Accumulating data show that nitrates may attenuate platelet adhesion and aggregation.[45]

A meta-analysis of trials undertaken before the widespread use of thrombolytics and using intravenous nitrates within 24 hours of the onset of symptoms of acute MI revealed a 35% reduction in mortality.[35] The use of nitroglycerin was found to be superior to that of sodium nitroprusside. Additional studies with nitrates have shown notable reductions in the incidence of infarct extension and expansion, cardiogenic shock, and left ventricular thrombus formation.[47] In the GISSI-3 megatrial, the use of intravenous nitrates for 24 hours, followed by transdermal or oral therapy, failed to show an effect on six-week mortality (Table 6).[35,41,42,46] Similarly, when the use of oral mononitrate was compared with that of placebo in the large ISIS-4 study, no benefit was demonstrated in reducing mortality.[43] The routine use of intravenous nitroglycerin in patients with acute MI, therefore, remains unresolved and warrants further study, particularly in the light of the finding that the group treated with the combination of nitrates and lisinopril in the GISSI-3 study had the lowest overall mortality (6.0%).[42]

Intravenous nitroglycerin remains a valuable agent to lessen pain and lower the blood pressure early on in the development of acute MI and may have a salutory effect on the incidence of heart failure or pulmonary edema complicating the acute event.

Care should be taken when titrating the dosage of intravenous nitrates to avoid rebound tachycardia and hypotension—offsetting any potential benefits—by increasing myocardial oxygen demand and decreasing coronary perfusion pressure, respectively. Additional problems may be encountered in patients with right ventricular infarction, in whom venodilation and pooling may reduce venous return, dramatically reducing cardiac output. About 10% of patients have sensitivity to nitrates, thought to be vagally mediated. This is particularly prominent in patients with inferior wall infarction, in whom even small doses can cause profound hypotension, bradycardia, or both. Last, continuous and prolonged use results in the development of tolerance and the attenuation of the hemodynamic effects. This can be obviated by a transient interruption of therapy.

Calcium Channel Blockers

Calcium channel blockers constitute a heterogeneous group of compounds that have in common the ability to block calcium ion transport across membranes of cardiac and smooth muscle by inhibiting the slow channels. They reduce myocardial oxygen ventilation rate by vasodilation and afterload reduction and by exerting a negative inotropic effect on myocardium. Most of these agents are powerful coronary vasodilators, but some have a negative chronotropic effect by their action on sinoatrial node function.[35] Calcium influx appears to be an important mechanism in cell injury during reperfusion, and experimental data have suggested that such injury may be attenuated by the previous administration of calcium channel blockers.[48] Based on the aforementioned effects, these agents appear to have the theoretical credentials to render them useful adjuncts in the treatment of patients with acute MI. Negative inotropism and peripheral vasodilation may result in hypotension, rebound tachycardia, and a reduction in coronary perfusion pressure, thereby negating possible benefits.

The calcium channel blockers vary widely in their spectrum of tissue specificity and intensity of hemodynamic effect. Therefore, different agents or classes should be discussed independently with regard to their efficacy in patients with acute MI.

Nifedipine. Nifedipine has been evaluated in a number of trials involving patients with acute MI. In the Trial of Early Nifedipine in acute myocardial infarction (TRENT) study, nearly 4,500 patients were randomly assigned, within 24 hours of their MI, to treatment with sublingual, followed by oral, nifedipine for 28 days, or to placebo.[49]

TABLE 6.—*Mortality Data on the Use of Nitrates in Acute Myocardial Infarction**

Treatment Trial	Patients, %		P Value
	Nitrates	Control	
Intravenous†	13.3	18.9	.001
Oral‡	10.0	12.3	NS
GISSI-3§	6.5	6.9	NS
ISIS-4‖	6.9	7.2	NS

NS = not significant

*From Held et al,[34] the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3 (GISSI-3) Research Group,[40] Ferguson,[41] and the Fourth International Study of Infarct Survival (ISIS-4) Collaborative Group.[42]

†Ten trials from the prethrombolytic era were pooled.

‡Five trials were pooled.

§In the GISSI-3 trial, nitrates were given intravenously and transdermally.

‖In the ISIS-4 trial, oral mononitrates were given.

The mortality at one month was 10.2% in the treatment group and 9.3% in the placebo group (NS). In addition, there was a trend to an increased incidence of reinfarction in the treated group. The Secondary Prevention of Reinfarction Israeli Nifedipine Trial (SPRINT-II) was prematurely terminated because of an increase in the early mortality in the patients treated with nifedipine compared with controls (15% versus 13%).[50]

Verapamil. The use of verapamil was evaluated in the Danish Study Group on Verapamil in Myocardial Infarction trial.[51] Patients were randomly assigned to receive placebo or intravenous, followed by oral, verapamil within 48 hours of the onset of acute MI. At six months' follow-up, the mortality rate in treated patients did not differ from that of controls (12.8% versus 13.8%; P = NS). In addition, the enzymatically determined infarct size and reinfarction rate did not differ in the two treatment groups. Verapamil may be of benefit in treating supraventricular tachyarrhythmias in patients with acute MI, particularly if other antiarrhythmic agents are inadvisable and neither ventricular function nor the conduction system is jeopardized.

Diltiazem. The use of diltiazem was evaluated in the Multicenter Diltiazem Post-Infarction Trial (MDPIT) Research Group, which randomly assigned nearly 1,500 patients within 2 to 15 days of infarction to a secondary placebo-controlled trial.[52] At a mean follow-up of 25 months, there was no reduction in mortality in the diltiazem group. A post hoc analysis indicated that the use of diltiazem increased the incidence of cardiac events in those patients who had radiographic evidence of pulmonary congestion and decreased it in those who did not.

Pooled analysis of the 21 controlled trials of calcium channel blockers in patients with acute MI revealed an excess mortality of 6% in the treatment group, with a 95% confidence limit that includes a 4% benefit but as much as an 18% increase in mortality.[35] Therefore, the routine use of these agents in patients with MI cannot be endorsed.

Other potentially favorable interventions in acute MI have been the subject of controversy. These include the routine use of magnesium and prophylactic lidocaine.

Magnesium

Magnesium has several possible cardioprotective effects in patients with acute MI. This agent may attenuate catecholamine-induced myonecrosis; inhibit calcium influx into myocardial cells; have an antiarrhythmic potential; reduce coronary vasospasm, peripheral resistance, and afterload; and decrease platelet adhesiveness. Promising data in animals revealed both a reduction in infarct size and an increase in the threshold for the electrical excitation of cells.[53] This prompted eight relatively small randomized trials involving the intravenous administration of magnesium in patients with acute MI.[54] The pooled results showed an encouraging 36% reduction in the odds of death when magnesium therapy was used compared with placebo. An important note is that these studies were initiated before the widespread use of thrombolytics.

The recently completed ISIS-4 trial incorporated a group of patients who received an 8-mmol bolus of intravenous magnesium followed by an infusion of 72 mmol over the next 24 hours. The 35-day mortality rate was 7.3% in the magnesium-treated patients and 6.9% in the controls (P = NS).[42] Thus, the routine administration of this agent to all patients with acute MI cannot be endorsed; it remains useful for special situations, such as the management of torsades de pointes.

Lidocaine

Ventricular ectopy is common in the early hours after an MI, and ventricular tachycardia and fibrillation contribute substantially to death during this vulnerable period. Because lidocaine is efficient at suppressing ventricular arrhythmias in patients with ischemia, it has been speculated that the routine prophylactic use of this agent may afford an advantage in terms of survival.

To date, 14 randomized trials have used prophylactic lidocaine, intravenously or intramuscularly, in the first 48 hours after an MI.[55] Although the pooled data from these studies did indeed indicate a 35% reduction in the odds of developing ventricular fibrillation, this was offset by an increased incidence of asystole of a similar magnitude, such that there was no important effect on mortality and even a suggestion of harm in the actively treated group. These data, together with the drug's negative inotropic action and neurologic side effects, mitigate against the routine use of prophylactic lidocaine in all patients with acute MI, particularly where facilities for the detection and treatment of ventricular arrhythmias are available. Lidocaine, however, remains the therapeutic agent of choice for ventricular tachycardia and fibrillation in these patients.

Conclusion

During the past decade, the management of acute myocardial infarction has evolved from that of circulatory support and arrhythmia detection and treatment to one of aggressive early intervention aimed at reperfusion and improved survival and quality of life. Based on the data available from numerous randomized, controlled trials,

the following management strategy is proposed for all patients with acute MI, provided there are no contraindications to the use of a specific therapy.

An intravenous thrombolytic agent should be administered to all eligible patients presenting within 6 hours of the start of symptoms. The time window can be extended for as long as 12 hours in patients who have evidence of stuttering evolution of their infarct. Scientific evidence now exists to endorse front-loaded tPA as the optimal thrombolytic regimen, particularly in younger patients with anterior-wall infarction. The ongoing economic debate continues to rage as to whether its margin of benefit over streptokinase justifies the routine use of this more expensive agent. The use of aspirin results in additional benefit in reducing the incidence of reinfarction, stroke, and death, without an increase in major hemorrhagic complications. All patients should receive 160 to 325 mg when the diagnosis is suspected and daily thereafter. The conjunctive use of intravenous heparin (5,000 units) reduces the incidence of reocclusion and improves survival, especially when tPA is used as the lytic agent. The heparin should be administered concurrently with the tPA, and the subsequent infusion, titrated according to the activated partial thromboplastin time, continued for at least 72 hours.

Direct PTCA serves as a useful alternative to thrombolysis in institutions with the facilities for, and operators skilled in, performing the procedure. It is the reperfusion method of choice when contraindications to thrombolysis exist or when the acute infarct is complicated by cardiogenic shock. Coronary artery bypass grafting, although feasible and safe in selected institutions in patients with evolving MI, should generally be reserved for patients in whom PTCA has failed or those at high risk because of their coronary anatomy.

Intravenous, followed by oral, β-blockade imparts a survival advantage and a decreased incidence of reinfarction, nonfatal cardiac arrest, nonfatal stroke, and recurrent ischemia. Angiotensin-converting enzyme inhibitors reduce mortality and can be administered safely in the early phase of evolving infarct. Intravenous nitroglycerin attenuates ischemic pain and confers additional benefit in those patients with pulmonary congestion complicating the acute ischemic insult. Additional studies are probably required to define its exact role in reducing mortality.

The routine use of calcium channel blockers, lidocaine and prophylactic antiarrhythmic agents, intravenous magnesium, and immediate or deferred angioplasty in the absence of demonstrable postinfarction ischemia cannot be advocated in patients with acute MI.

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Articles

Herniography in Symptomatic Patients Following Inguinal Hernia Repair

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Patients with symptoms at the site of a previous inguinal hernia repair may constitute a diagnostic dilemma. The usefulness of herniography in the assessment of these patients was evaluated at 54 symptomatic sites in 46 subjects. Ten persistent or recurrent hernias were shown by herniography, only 2 of which were definitely detected on physical examination. The herniogram was normal at 44 sites, of which, on physical examination, 5 were equivocal and 1 was diagnosed as a definite hernia. On the unoperated-on or asymptomatic side, a total of 14 hernias were shown herniographically. Of these hernias, 8 were not detected on physical examination. Herniography was found to be more sensitive than physical examination in detecting hernias at the symptomatic, previously operated-on sites, as well as at the unoperated-on or asymptomatic sites. When a herniogram provides corroborative evidence that hernia has not recurred, the need for reexploration may be eliminated.

(Hamlin JA, Kahn AM: Herniography in symptomatic patients following inguinal hernia repair. West J Med 1995; 162:28-31)

Patients who have undergone inguinal hernioplasty or herniorrhaphy may present with persistent or recurrent symptoms. Occasionally these symptoms are caused by recurrence of the hernia. Recurrent hernias may be difficult to detect on physical examination.

Herniography provides a method whereby the peritoneal fossae and possible herniations can be detected radiographically.[1-7] In patients in whom the findings of a physical examination are inconclusive or when the symptoms and physical findings are discordant, the information provided by the herniogram is helpful in clinical decision making (Figure 1).

We report our radiographic technique and the results of herniography in patients who previously had hernias repaired but who experienced persistent or recurrent inguinal pain.

Patients and Methods

Patients are asked to empty their bladders just before lying on the fluoroscopic table. If necessary, hair is shaved from a small area of the anterior abdominal wall midway between the umbilicus and the pubic symphysis. This area is cleaned with an iodophor detergent and draped with a fenestrated sheet. A solution of sodium bicarbonate (1 ml) and 1% lidocaine (9 ml) is used for anesthesia in the skin and subcutaneous tissue in the midline. A 20-gauge spinal needle is then inserted into the peritoneal cavity through which 50 ml of nonionic contrast material (320 mg per ml of organically bound iodine) is administered.[8] Fluoroscopy is used to confirm the intraperitoneal deposition of contrast material and monitor the injection. After the needle is removed, a small bandage is applied.

The table is raised to an erect position. The patient is turned and then lowered in a prone position, with the head of the table elevated to 25 degrees, permitting the contrast material to flow into the inguinal fossae. The table is again elevated for spot filming of the inguinal fossae in the erect position (frontal and both oblique projections). While the patient is facing the table, a sponge pad is placed between the thighs and table so that when the table is again lowered to the previous 25-degree position, the inguinal area is elevated from the table. In this position, two overhead posteroanterior films centered at the groin are taken: 90 degrees to the table top and 35 degrees cephalic angulation. All films are taken with the patient straining.

The radiographs are interpreted in accordance with previously described criteria.[1-5]

Results

In a 24-month period, we saw 88 patients for herniography. Among these patients, 43 had a previous inguinal hernia repair and had persistent or recurrent pain or swelling at the surgical site. Of these 43 patients, 39 were men. Their average age was 41 years (range, 21 to 75 years). Three of these patients had a second herniogram for evaluation of pain following another hernia operation. Because there was surgical intervention between herniograms, each of these three patients was considered

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Figure 1.—This 42-year-old man had bilateral inguinal pain. The results of a physical examination of the inguinal canals were negative on the left and equivocal for hernia on the right. Herniography revealed no hernia on the right and an indirect hernia on the left, thereby indicating on which side a hernia operation should be considered.

Figure 3.—A 39-year-old man who had previously undergone repair of bilateral complex inguinal hernias presented with groin pain bilaterally. The physical examination showed no abnormalities on the right and was equivocal for a hernia on the left. The herniogram showed a recurrent indirect inguinal hernia on the left (angled view) and no recurrence on the right.

two subjects. Therefore, the total number of subjects seen for evaluation was 46.

Bilateral hernia repairs had previously been done in 15 subjects: 8 had bilateral symptoms, and 7 were symptomatic on only one side. In these 7, herniographic findings on the asymptomatic side were considered incidental. Thus, in 46 subjects, 54 symptomatic sites of previous inguinal hernia repair sites were evaluated.

The physical examination and herniographic findings of the 54 sites were concordant at 40 sites, with both examinations finding no hernia at 38 sites and both revealing a recurrent or persistent hernia at 2 sites. At 7 sites the herniogram demonstrated a hernia that was not detected on physical examination (Figure 2) whereas at one site the results of the physical examination were positive for a hernia, but the herniogram was normal. The findings of the physical examination were equivocal at 6 sites; of these, the herniogram was normal in 5 and showed a hernia at only 1 site (Figures 3 and 4).

Figure 2.—A 33-year-old man had pain at the site of a previous right inguinal herniorrhaphy. No hernia could be palpated on physical examination. An irregular direct inguinal hernia sac was demonstrated on the right.

There were 31 inguinal areas that had not been previously operated on, plus 7 that had undergone a previous repair, but the patients were asymptomatic. The physical examination and herniogram results were concordant at 25 sites. At 10 sites where the physical examination showed no abnormalities, the herniogram revealed a hernia at 8 and was equivocal at 2. The physical examination findings were equivocal at 3 sites where the herniogram was negative (Figure 5).

Six of the subjects had hernia operations following the herniogram. The interval between the herniogram and subsequent surgical repair ranged from 3 to 263 days. One of these subjects had previous bilateral hernias repaired but was only symptomatic on one side. Two of the subjects had physical examination findings suggestive of a recurrent hernia on the symptomatic side, only one of which was confirmed by herniography. In the other four subjects, the physical examination showed no abnormalities on the symptomatic side, but the herniogram was interpreted as demonstrating a recurrent hernia in two.

On the unoperated-on or asymptomatic side in these six subjects, two hernias were diagnosed by physical examination and confirmed by herniography. Herniography detected one hernia that was not evident on physical examination, and in two subjects both the physical examination and herniogram were negative. In the sixth patient the physical examination findings were equivocal, but no hernia was found by herniography.

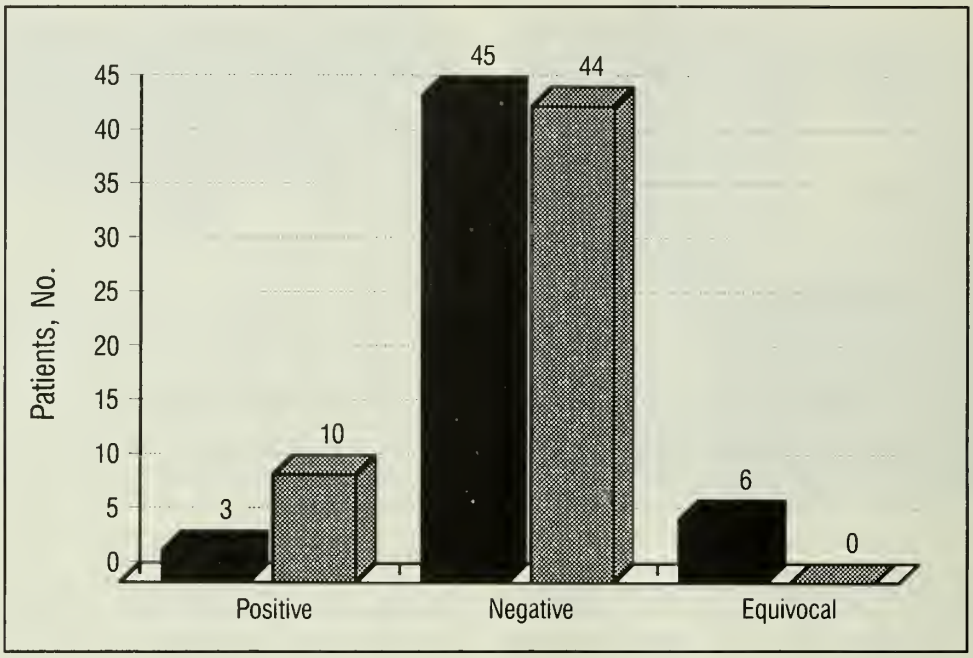

Figure 4.—The findings of physical examinations (**black bars**) are compared with those of herniograms (**gray bars**) at 54 symptomatic sites of previous inguinal hernia repair.

Among these six subjects, one had a bilateral repair enabling a correlation between the herniographic and surgical findings at seven sites. Four hernias diagnosed by herniography were confirmed at surgery and repaired. In two subjects the herniogram was normal, but the symptoms were so compelling that the inguinal areas were explored and no hernia was found. At the one site where the herniographic and surgical findings were discordant, there had been a previous inguinal exploration and excision of a lipoma of the spermatic cord. The herniogram was interpreted as demonstrating a hernia, but as none was found surgically, this was a "false-positive" herniogram.

A maculopapular rash developed in one patient approximately 24 hours after the herniogram, which may have been related to the contrast material. No other complications occurred in this series. Possible complications include contrast material reaction, peritonitis, abscess, or hematoma of the abdominal wall or viscera. No contrast material was injected into a viscus or blood vessel. The incidental administration of 1 to 5 ml of contrast material into the anterior abdominal wall, omentum, or mesentery is recognized by fluoroscopy and indicates the need to reposition the needle. These injections are asymptomatic, and their frequency was not recorded.

Discussion

Herniography is a well-established modality used to examine the inguinal fossae.[1-6] The inguinal fossae are defined by the peritoneal ridges that occur on the lower anterior abdominal wall. Anatomists and authors have not agreed on the nomenclature of these ridges and fossae,[2,5,6] and therefore, in identifying them, we indicate the structures that produce them. Between the medial umbilical fold (urachus remnant) and the paired lateral umbilical folds (umbilical artery remnants) are the supravesical fossae. The medial inguinal fossae lie between the lateral umbilical folds and the epigastric folds (produced by the inferior epigastric vessels), lateral to which lie the lateral inguinal fossae. These folds and fossae can be variably identified by positive-contrast peritoneography.[5] The folds have also been identified by negative contrast in patients with pneumoperitoneum.[9]

A smoothly marginated extension of contrast material beyond the limits of the inguinal fossa represents a hernia. An indirect inguinal hernia protrudes from the lateral inguinal fossa, lateral to the epigastric fold, and extends along the inguinal canal. A direct inguinal hernia protrudes from the medial inguinal fossa, medial to the epigastric fold, with an axis perpendicular to the inguinal ligament.

Our technique for performing herniography varies from that of others in needle placement. The left lower quadrant, at the lateral border of the rectus abdominis muscle, has been recommended as the location for entering the peritoneal cavity.[1-3,5,6] Because the lateral border of the rectus abdominis muscle may be difficult to identify, and to avoid the unintentional pricking of the inferior epigastric artery or vein, we think the midline subumbilical approach is preferable.

In our subjects, a hernia was demonstrated at 18.5% of the symptomatic sites. This is less than the 35% to 42% previously reported.[4,10] The herniogram was normal at 44 of the symptomatic sites and revealed a persistent or recurrent hernia at 10 sites. Of those 10 hernias, only 2 were diagnosed on physical examination. One patient diag-

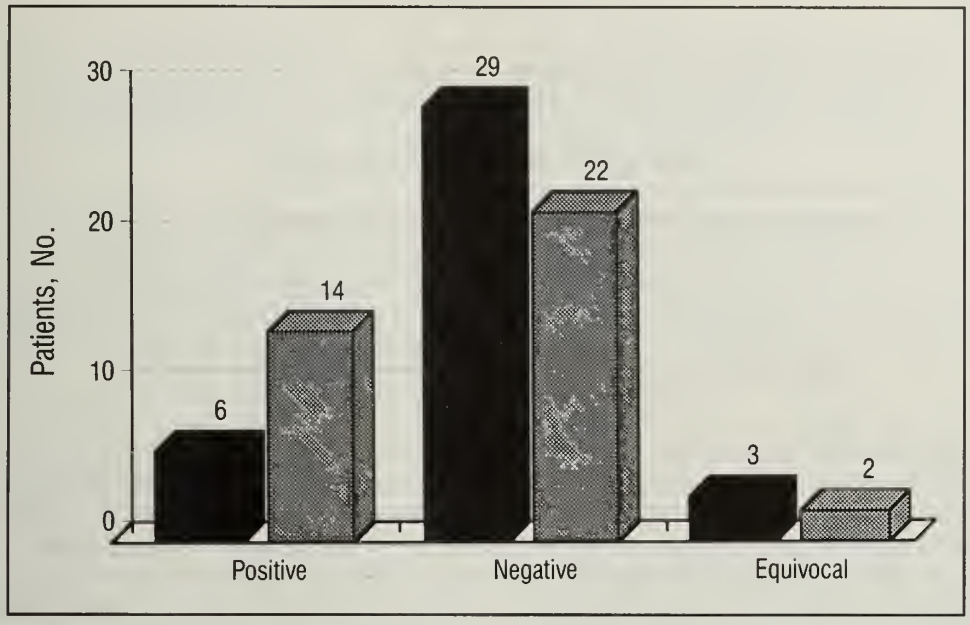

Figure 5.—The findings of physical examinations (**black bars**) are compared with those of herniograms (**gray bars**) on the unoperated-on side (31 sites) or the asymptomatic previously operated-on side (7 sites).

nosed with a persistent or recurrent hernia on physical examination did not have a hernia on herniography. The herniogram was, therefore, useful for identifying those patients whose symptoms could be associated with persistent or recurrent hernias who might benefit from reexploration. Conversely, by demonstrating the absence of a hernia, some of these patients were undoubtedly saved a second operation.

On the unoperated-on or asymptomatic side, the herniogram confirmed the hernias detected on physical examination in six subjects. Eight additional hernias were discovered by herniography that were not detected on physical examination (Figure 5). Herniography would appear, therefore, to be more sensitive than physical examination in detecting hernias.

Six subjects underwent seven inguinal explorations following herniography. The other patients with hernias had not yet decided on another hernia operation or had sought medical care elsewhere and were unavailable for follow-up. Of the seven explorations, four were at the sites of symptoms following previous herniorrhaphies. The herniographic and surgical findings were concordant in three of the four. At two sites, surgical procedure confirmed the hernia demonstrated radiographically. At one site, the herniogram was normal, but compelling symptoms led to surgical intervention, and no hernia was found. The one site with discordant findings was the false-positive herniogram that occurred in a patient with anatomic distortion from a previous operation. Hernias were demonstrated on the previously unoperated-on side in three subjects and confirmed surgically in each. One of these hernias was not detected on physical examination. The true incidence of falsely positive and falsely negative herniograms will require a much larger number of patients who come to surgery following herniography.

Herniography is valuable in the postoperative evaluation for persistent symptoms in patients who do not have clinically detectable hernias on physical examination.[4,10] When the radiographic information provides corroborative evidence that hernias have not recurred, the need for reexploration may be eliminated. The herniogram also allows the identification of patients in whom recurrent hernias have developed that are not detected on physical examination.

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Articles

How Well Do Older Persons Tolerate Moderate Altitude?

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We studied the physiologic and clinical responses to moderate altitude in 97 older men and women (aged 59 to 83 years) over 5 days in Vail, Colorado, at an elevation of 2,500 m (8,200 ft). The incidence of acute mountain sickness was 16%, which is slightly lower than that reported for younger persons. The occurrence of symptoms of acute mountain sickness did not parallel arterial oxygen saturation or spirometric or blood pressure measurements. Chronic diseases were present in percentages typical for ambulatory elderly persons: 19 (20%) had coronary artery disease, 33 (34%) had hypertension, and 9 (9%) had lung disease. Despite this, no adverse signs or symptoms occurred in our subjects during their stay at this altitude. Our findings suggest that persons with preexisting, generally asymptomatic, cardiovascular or pulmonary disease can safely visit moderate altitudes.

(Roach RC, Houston CS, Honigman B, et al: How well do older persons tolerate moderate altitude? West J Med 1995; 162:32-36)

In recent years more and more older men and women have sojourned at moderate altitudes—2,000 to 3,000 m (6,500 to 9,800 ft)—for recreation or work, but little attention has been given to the effect of age or existing disease on their tolerance for altitude. Older visitors might be expected to be at greater risk for acute mountain sickness (AMS) because of underlying cardiovascular or pulmonary disease or the normal processes of aging. They might also risk exacerbation of their underlying diseases. Although this risk appears to be small,[1-3] practicing physicians have little data on which to base advice to their older patients. We studied a group of older men and women visiting a mountain resort at 2,500 m (8,200 ft) to determine their susceptibility to AMS and to examine their cardiovascular and pulmonary physiologic responses and clinical signs and symptoms over a five-day period at moderate altitude.

Study Group and Methods

We randomly selected 105 persons from the first 500 men and women who registered for the 50th reunion of the United States Army Tenth Mountain Division in Vail, Colorado (altitude 2,500 m). The reunion site was chosen because of its proximity to Leadville, Colorado, and the former location of Camp Hale, where the Tenth Mountain Division trained during World War II. Of the 105 men and women, 8 were excluded because of scheduling conflicts or incomplete data, leaving 97 for study. No one was excluded for reasons of health. All signed informed-consent forms approved by the Colorado Multiple Institutes Review Board of the University of Colorado Health Sciences Center, Denver.

Data Collection

Before they arrived in Vail, subjects completed a questionnaire that included the altitude of their residence; their history of hypertension, heart or lung disease, diabetes mellitus, or smoking; their usual exercise pattern; and their self-rated fitness. On arrival in Vail (day 0), participants were briefed and given a questionnaire on activities, symptoms of AMS, and other health-related symptoms. These same questions were answered each day of the study. Symptom scores for AMS were tabulated using graded (0 to 3) self-evaluation of headache, sleeplessness, fatigue, light-headedness, and gastrointestinal symptoms; AMS was defined as a score of 3 or higher, including at least one point for headache.[4] Subjects were then asked if they had had any of the fol-

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ABBREVIATIONS USED IN TEXT

AMS = acute mountain sickness
ANOVA = analysis of variance
ECG = electrocardiogram
Sao_2 = arterial oxygen saturation

lowing during the previous 24 hours: difficulty breathing, palpitations, or chest pain. If they had, they were asked whether these affected their activity and if they took medications for relief. The final question was how many alcoholic drinks were consumed in the past 24 hours. On day 0, we asked about previous altitude exposure and altitude illness. We also maintained logs at the local hospitals and physician offices to determine if any of our subjects required medical attention.

Beginning on day 1, those studied reported to one of six identical stations for testing on each of the first three days (days 1 to 3) and again on either the fourth or fifth day (recorded as day 4). After completing the daily questionnaire, participants rested supine for four minutes before a 12-lead electrocardiogram (Marquette, Model #MAC PC), blood pressure (Colin Medical Instruments Model BP-8800p), pulse rate, and arterial oxygen saturation (Sao_2; Ohmeda Model #3700 pulse oximeter) were recorded. Blood pressure, pulse rate, and Sao_2 measurements were repeated a minute later, and the two readings were averaged. Electrocardiograms were read independently by each of two cardiologists and assessed for abnormalities and changes from tracings taken in Vail on previous study days. Abnormalities were defined according to the Minnesota code.[5]

Pulmonary function was assessed using identical electronic spirometers (Spirometric Flowmate II) that were calibrated twice a day. After cardiovascular measurements were completed, those studied were seated, with nose clips in place; repeated measurements were made, and the best of at least three attempts was recorded. Measurements included forced vital capacity (% predicted[6]), one-second forced expiratory volume (% predicted[6]), and peak expiratory flow (liters per minute).

Medical histories, historical heart rate, blood pressure values, and ECGs were requested retrospectively from the personal physicians of those studied. The presence of underlying long-term diseases was determined by these reports and verified by physician questionnaire in 98% of those studied. Data were reported using the self-reports. If a discrepancy existed, the physician questionnaire was used.

TABLE 1.—*Subject Characteristics (mean ± SE) and Health History Provided by Personal Physicians*

Characteristic	Subjects: Men (n=77)	Subjects: Women (n=20)	US Population*
Age, yr	70.7±0.5	66.7±1.1	32
Height, cm	175.6±0.8	163.6±2.0	
Weight, kg	82.6±1.5	69.9±3.3	
	No. (%)	No. (%)	%
Cardiovascular	19 (25)	0 (0)	27
Hypertension	27 (35)	6 (30)	37
Pulmonary	8 (10)	1 (5)	
Diabetes mellitus†	5 (6.5)	0 (0)	10
Current smokers	14 (18)	5 (25)	16
Former smokers	52 (67)	9 (44)	68
Self-assessed fitness			
Excellent	17 (22)	5 (25)	37
Good	44 (57)	10 (50)	32
Fair/poor	16 (21)	5 (25)	31

*From US National Center for Health Statistics, Vital and Health Statistics, Series 10, 1990.
†Taken from self-report questionnaire.

Statistical Analyses

Data were analyzed using repeated measures of analysis of variance (ANOVA) for analysis of day-to-day changes and two-way ANOVA for an analysis of changes between groups such as normotensive and hypertensive subjects. Post hoc pairwise comparisons were made using Tukey's post hoc test. Data are presented as the mean plus or minus the standard error of the mean (SE). A P value of less than .05 was considered significant.

Results

Of the 97 participants aged 69.8 (± 0.5 years; range, 59 to 83), 77 (79%) were men, and 81 (84%) lived at or near sea level. The characteristics of the study group are reported in Table 1. Of note, 19 (20%) of the participants had coronary artery disease, 33 (34%) had hypertension, 9 (9%) had lung disease, and 5 (5%) had diabetes mellitus. Of those studied, 76 (78%) considered themselves to be in good to excellent physical condition; 88 (91%) described themselves as moderately to very active before this visit, and the rest were usually inactive at home. Before arriving in Vail, 73 (75%) had stopped for 24 to 48 hours at a lower altitude (average elevation, 1,600 m [5,250 ft]), 22 (23%) had not stopped at an intermediate altitude, and 2 (2%) had stopped above 2,500 m (8,200 ft).

Incidence of Acute Mountain Sickness

Of the 97 persons studied, 16 (16%) had AMS at some time during their stay in Vail; for 11 of the 16, AMS occurred on day 0 or the next day. The remaining 5 cases occurred in the next two days. Acetaminophen or aspirin was used by 8 of the 16 with AMS; 1 took a sleeping pill to relieve symptoms. Of those with AMS, all had previously been to high altitude, and 7 had previously experienced altitude illness. Alcohol intake was not related to the incidence or severity of AMS. In fact, the 81 who did not have AMS had a greater alcohol intake than those who did ($P < .05$). Activity was mildly to moderately reduced in 8 of those with AMS and not at all in the remaining persons studied.

Of those who did not meet the criteria for AMS, 66 had no symptoms of altitude illness, 10 had one symptom, and 5 had two symptoms attributable to altitude. All but one had previously been to altitude, and 10 had

previously experienced altitude illness. Of those studied, 10 reported a mild reduction in activity because of their symptoms, and 9 took acetaminophen or aspirin for their symptoms.

At some time during their stay in Vail, 36 of the 97 persons studied (37%) had mild difficulty breathing; 23 (24%) had palpitations; and 11 (11%) had nonspecific chest pain. None of these symptoms were related to AMS or were severe enough to require medical attention.

Arterial Oxygen Saturation

The daily Sao_2 was 92% ± 0.1% over the five days at altitude, with less than 1% daily variation (Figure 1-A). Although the Sao_2 was not statistically different between those with and those without AMS ($P = .15$), there was a slight rise in the Sao_2 over the four days in those free of AMS and a slight fall in Sao_2 in those with AMS.

Spirometry

Forced vital capacity (% predicted) increased from day 1 on days 2 and 4 ($P < .01$) and showed the same trend on day 3 (Figure 1-B). Other spirometric measurements did not change over the time in Vail. For all those studied over the five days at Vail, the one-second forced expiratory volume was 91% ± 1% of predicted and the mean peak expiratory flow was 7.1 ± 0.1 liters per minute.

Cardiovascular Observations

On the subjects' arrival at Vail, electrocardiogram (ECG) results were normal in 59 (61%). In the remaining 38, a wide variety of abnormalities were noted; 19 (20%) had ECG abnormalities suggestive of coronary artery disease. These included Q waves, ST depression, left bundle branch block, and left anterior fascicular block. No clinically important changes were noted during serial ECG measurements in any of our subjects during their stay in Vail.

Of the 38 participants with ECG abnormalities identified on their arrival in Vail, previous ECGs were obtained from 21. Of these, 17 showed no changes between their historical ECGs and the ones taken in Vail. Of the remaining 4 participants, altitude ECG tracings in 2 revealed minor ST segment depression consistent with ischemia, and in the other 2 persons studied, atrial fibrillation was present. The importance of the changes from the historical records in these four is unclear because the ECG tracings before ascent were obtained one to three years before their arrival in Vail. No symptomatic events occurred in these four that indicated the presence of myocardial ischemia.

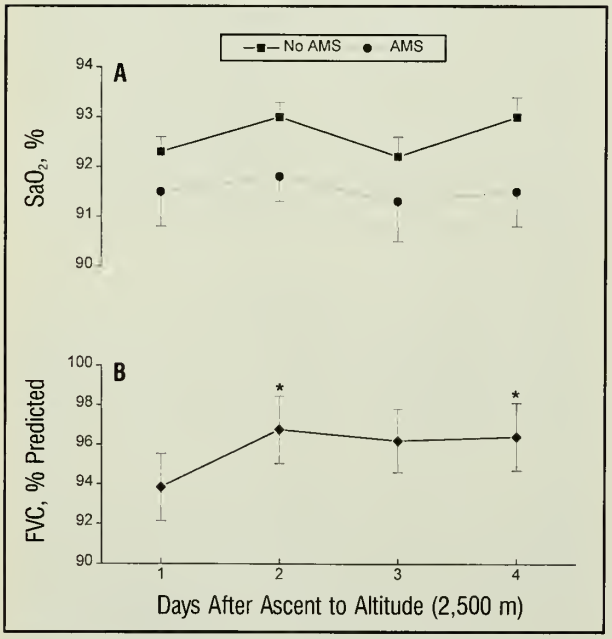

Figure 1.—**A,** The arterial oxygen saturation (Sao_2) in elderly visitors to moderate elevations (2,500 m [8,200 ft]) over a 5-day period in those with acute mountain sickness (AMS) is compared with Sao_2 values of those without AMS. Between-group differences were not statistically significant. **B,** A slight increase occurred in the forced vital capacity (FVC) in all subjects on days 2 and 4 ($P < .01$).

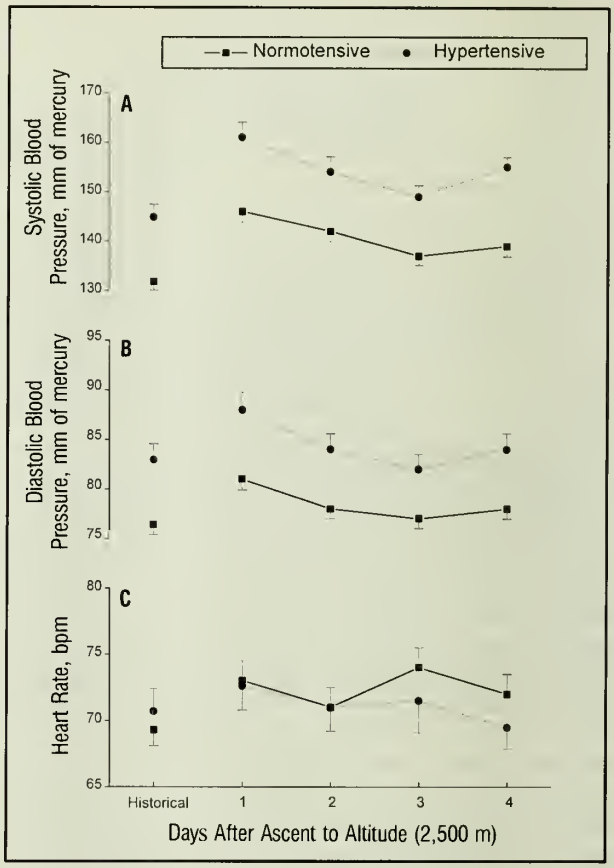

Figure 2.—**A,** Systolic and, **B,** diastolic blood pressure and, **C,** heart rate responses are shown in hypertensive and normotensive subjects on days 1 through 4 at 2,500 m (8,200 ft). Blood pressures decreased significantly on all days compared with day 1 ($P < .01$) in both hypertensive and normotensive subjects and were significantly higher on all days in the hypertensive group compared with the normotensive group ($P < .001$). Historical blood pressure values from each patient's physician (n = 95) are shown for comparison.

Apparently both systolic and diastolic pressures were increased on day 1 in Vail and then declined progressively over subsequent days at altitude in both normotensive and hypertensive persons studied (Figure 2-A and -B, $P < .01$). We obtained historical blood pressure values on 95 of the 97 participants. These values, predominantly from near sea level, were significantly lower than the day 1 values for both groups at Vail ($P < .05$, Figure 2-A and -B). When or under what conditions participants' blood pressure measurements were obtained by their physicians is not known. Heart rates did not differ significantly between hypertensive and normotensive groups and did not change over time in Vail. Of the 33 persons with hypertension, 28 were taking some combination of antihypertensive medication; only 1 is known to have increased his dose of antihypertensive medication while at Vail. The 5 with hypertension but not on a medication regimen maintained their blood pressures within normal values throughout their stay in Vail.

Of note, four participants with hypertension had systolic pressures above 180 mm of mercury or diastolic pressures above 110 mm of mercury on either day 0 or 1. In these four, the systolic pressure fell from 197 ± 7 mm of mercury on day 1 to 167 ± 5 mm of mercury (SE) on day 4, and the diastolic pressure fell from 101 ± 9 mm of mercury to 90 ± 6 mm of mercury ($P < .01$). Three other persons studied, not known to have hypertension, had systolic pressures above 180 mm of mercury on the first two days of the study; in all three, the pressure decreased to below 180 mm of mercury by day 3.

Discussion

This study represents to date the most comprehensive investigation of older persons visiting moderate altitude. The most important observation in this group is that active travelers with preexisting asymptomatic cardiovascular and pulmonary disease safely traveled to moderate altitudes without exacerbation of their disorders. Our data also suggest that the incidence of AMS was not higher in this group than in younger persons.

The 16% incidence of AMS in this group of older persons was slightly lower compared with previous reports on younger persons.[7-9] In fact, the symptoms were less severe and had less effect on the activities of those studied than expected from previous reports in younger persons.[7,8] Several factors may have influenced the lower incidence of AMS in our study. A brief stopover at a lower altitude may have contributed, although it has been shown that a stay of less than 38 hours has little effect.[8] Also, older persons tend to minimize their symptoms when completing a questionnaire.[10] Finally, our group might have been self-selected in that they felt able, based on previous experience, to go to this altitude. Nevertheless, the health history of this group is similar to that of other groups that visit similar altitudes for meetings and conferences, and we consider our findings applicable to the older traveling public.

In our previous study, we found that 16% of 410 visitors to moderate altitudes aged 60 to 87 had symptoms of AMS; the incidence of symptoms decreased linearly with increasing age.[8] This finding supported that of an earlier report that showed decreased severity of AMS with increased age in 278 trekkers studied at 4,243 m (13,920 ft) in Nepal.[11] In a study at altitudes comparable to Vail's, 25% of 454 health professionals (ages not given) visiting two mountain resorts at 2,100 m (6,890 ft) had symptoms of AMS at some time during the five days after arrival.[9] From these studies, we conclude that increasing age is associated with less severe symptoms of AMS.

Previous studies have suggested that older persons would show arterial oxygen desaturation and concomitant clinical signs and symptoms with exposure to high altitudes. One such study, conducted on the same six men 35 years apart, showed an increased alveolar-arterial oxygen gradient at altitudes above 3,100 m (10,170 ft).[12] Results from pulse oximetry showed that our participants were well oxygenated, however, and the results compared favorably with those from permanent, older residents at similar altitude.[13]

We found no important relationship between decreased pulmonary function and symptoms of altitude illness. In contrast, decreased vital capacity, assumed to be indicative of pulmonary interstitial edema, has been reported in young, healthy visitors to altitude ill with AMS at higher altitudes.[14-16] The gradual increase in forced vital capacity that we observed over time in Vail was noted by others.[17] A gradual increase in forced vital capacity was reported in four persons studied over seven days at 4,340 m (14,240 ft). These findings suggest that in the present study, pulmonary function was maintained and detrimental changes associated with higher altitudes were avoided.[14,15,17,18]

The prevalence of coronary artery disease in our group was estimated to be 20%. Despite the large amount of underlying cardiovascular disease, no adverse cardiovascular symptoms occurred as a result of exposure to moderate altitude. The apparently low risk of cardiovascular complications is supported by others[18-21] and by the advice that "going up into the mountains to trek or ski cross country is a safe undertaking for those who believe they are able to do this."

In previous studies, both systolic and diastolic blood pressures were increased after abrupt ascent to high altitudes in normotensive and hypertensive persons, but studies have been limited to younger persons.[2] Concern has been expressed that older persons who have a higher incidence of hypertension might be at greater risk at altitude.[2] In contrast to a previous study at a higher altitude that showed that diastolic pressures are elevated for many days after ascent,[16] we found a decrease after 24 hours, although both systolic and diastolic pressures remained above historical sea level values throughout the stay at altitude.

Conclusions

It is generally safe for older men and women, including those with underlying asymptomatic heart and lung

disease, to make short visits to moderate altitudes. Asymptomatic coronary artery disease, hypertension, or pulmonary disease were not exacerbated in a clinically important way, did not result in adverse medical consequences, and did not limit the activity of the persons in our study. We suggest that hypertension is not a contraindication for visiting moderate altitudes; however, blood pressure should be monitored and antihypertensive medication regimens at sea level should be maintained. The incidence of AMS is certainly not higher than in younger persons and may be lower. Age alone is not a contraindication for a short visit to moderate altitude.

Acknowledgment

We gratefully acknowledge the enthusiastic participation of members of the Tenth Mountain Division attending their 50th reunion in 1992. Jerilu Atkins planned the logistics and participated in the study, and Chip Woodland, MD, Jill Beyer, MD, and Erica Perkins provided support. The Aspen Foundation, the Summit Foundation, the Vail Valley Foundation, the Tenth Mountain Foundation, and several other persons provided funding for this study. Marquette Electronics (Milwaukee, Wisconsin), Colin Medical Instruments (San Antonio, Texas), Spirometrics (Auburn, Maine), Graphics Control (Tustin, California), and Ohmeda (Louisville, Colorado) generously lent us their equipment.

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Conferences and Reviews

Dizzy Patients
Diagnosis and Treatment

Discussant
STEVEN R. McGEE, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Jonathan Drachman, MD, Chief Medical Resident; Henry Rosen, MD, Professor and Associate Chair; and Paul Ramsey, MD, Professor and Chair of the Department of Medicine.

Two years after his historic orbital space flight, and in the middle of his campaign for the United States Senate, Lieutenant Colonel John H. Glenn Jr accidentally fell and struck the left side of his head on a bathtub, causing disabling dizziness and nausea that confined him to bed for months and eventually forced him to pull out of the Senate race (R. Witkin, "Glenn Quits Race in Ohio, Citing His Slow Recovery," *New York Times*, March 31, 1964, pp 1, 18, 19). At a news conference announcing his withdrawal, a panel of physicians reassured the world that Glenn's dizziness, despite rumors, was unrelated to space travel but instead resulted from trauma to the inner ear, a relatively routine condition that only time would heal. As if to challenge the notion that dizziness was untreatable, hundreds of dizzy patients then wrote to the colonel, expressing sympathy and encouraging him to try a variety of cures, each provided with its own testimonial: "Drink whiskey before going to work," "Take vitamin B_{12} or vitamin C," "Drink large volumes of pineapple juice," "Ask for electric shocks behind the ear," "Read the book *I Believe in Miracles*," "Attach a gyroscope to the hip," and "Whatever else (the colonel does), stay away from those little blue and white pills Antivert [meclizine hydrochloride]."[1]

These folk remedies are a reminder that dizziness, despite its prevalence, often frustrates and confounds both physicians and patients. Dizziness accounts for 1% of visits to US office-based physicians.[2] Of patients older than 60 years, 20% have experienced dizziness severe enough to affect their daily activities.[3,4] Among dizzy patients who seek help, almost 70% initially see general internists or family practitioners, only 4% are referred to specialists, and 90% leave the physician's office with a prescription, most often for meclizine.[2] In this review I discuss the common causes of dizziness and provide a simple yet scientific approach to diagnosis and management.*

*See also the editorial by K. Kroenke, MD, "Dizziness in Primary Care," on pages 73-74 of this issue.

Diagnosis

Table 1, which is compiled from four prospective studies on dizziness,[5-8] emphasizes several points. First, among patients with dizziness who consult general practitioners, three diagnostic groups account for more than 75% of the final diagnoses: peripheral vestibular disorders, psychiatric disorders, and multiple sensory deficits.[5,6] Second, central vestibular disorders—such as brain-stem and cerebellar ischemia—may cause as much as 23% of cases of dizziness in older patients.[7] Third, hypotension is an uncommon cause of chronic dizziness in the clinic setting, but is responsible for 16% of the cases of dizziness seen in emergency departments.[8] Finally, only 8% to 14% of cases remain undiagnosed after thorough evaluation.

Peripheral Vestibular Disorders

Vertigo is a type of dizziness characterized by sensations of movement (twirling, tumbling, or tilting) felt inside a person's head. Vestibular disorders, either peripheral (inner ear) or central (brain stem, cerebellum), all cause vertigo that is episodic and of abrupt onset. Helpful distinguishing features are the duration of vertigo, the precipitating factors, and the associated symptoms.

Patients with benign positional vertigo (BPV) describe episodic vertigo lasting less than a minute, brought on by movements of the head—such as rolling over in bed, hyperextension of the neck, or bending over—and without other associated symptoms.[9,10] In all, 15% to 50% have had recent ear trauma or infection.[9-13]

The Hallpike-Dix maneuver, historically the key diagnostic test of BPV, is illustrated and described in Figure 1.[10-16] Although a positive test is usually required for diagnosis, the sensitivity of the maneuver was only 60% in one study of 250 patients with symptoms of BPV.[17] Of the initially negative tests, 30% became positive during subsequent clinic visits,[17] and once documented, a positive test was not present during every visit.[9] Few elderly pa-

(McGee SR: Dizzy patients—Diagnosis and treatment. West J Med 1995; 162:37-42)

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TABLE 1.—*Causes of Dizziness in 4 Studies*

Cause, %*	Study: Drachman and Hart[3] (n = 102)	Kraenke et al[6] (n = 100)	Slaane and Balah[7] (n = 116)	Herr et al[8] (n = 125)
Setting	Dizziness clinic	Walk-in clinic	Neurotology clinic†	Emergency department
Peripheral vestibular disease	38	43	46	43
Benign positional vertigo	12	16	23	- -
Vestibular neuronitis	9	3	8	- -
Meniere's syndrome	3	4	8	- -
Other	14	20	7	- -
Psychiatric	24	16	9	11
Multiple sensory deficit	13	2 (17)‡	2	1
Central vestibular disorder	7	10	23	6
Cardiovascular disease§	4	6	3	16
Unknown	9	8	14	10

*Totals do not equal 100% because miscellaneous diagnoses are excluded.
†Aged 70 and older.
‡Multiple sensory deficits were primary cause in 2% and primary or contributory cause in 17%.
§Hypotension—for example, orthostatic, vasovagal, arrhythmia-induced.

tients tolerate hyperextension of the head over the table edge; therefore, many clinicians allow a patient's head to land squarely on the table. Movement from seated to supine should occur over two seconds, with slower movements reducing the sensitivity of the test.[18]

Aside from confirming the diagnosis of BPV, a positive Hallpike-Dix maneuver also distinguishes BPV from central positional vertigo, an uncommon disorder usually caused by cerebellar tumors, carcinomatous cerebellar degeneration, or multiple sclerosis.[19-21] Table 2 reviews the three features—latency, adaptation, and fatigability—that may be helpful in differentiating these disorders.

Benign positional vertigo is commonly postulated to result from damage to the delicate sensory units of the inner ear, the semicircular canals and otolith organs. The three semicircular canals (anterior, posterior, and horizontal) normally detect spinning movements (that is, angular acceleration). Hair cells in each canal respond to rotation in a plane parallel to the canal by bending with the endolymph currents generated. The sensory units of the two otolith organs, saccule and utricle, differ in that they are denser than the surrounding endolymph. Embedded in a gelatinous membrane coated with calcium carbonate crystals (otoliths), these hair cells bend with gravitational forces (that is, linear acceleration), enabling the detection of positions or movements that tilt away from the vertical or horizontal planes. In patients with BPV, otoliths from the utricle become dislodged, perhaps because of recent ear trauma or degenerative changes, and settle to the most dependent portion of the inner ear, the posterior semicircular canal. With the posterior canal now abnormally burdened by otoliths, any movement in a plane parallel to the posterior canal (such as with the Hallpike-Dix maneuver) will produce exaggerated movement of the hair cells in that canal, provoking vertigo and nystagmus. The several-second latent period that is observed (Table 2) may reflect the time necessary to generate these exaggerated endolymph currents. "Fatigability" may occur because repeated head movements disperse otoliths throughout the endolymph system and away from the posterior canal.[18]

Evidence that BPV arises from the posterior semicircular canal includes the following: stimulation of the undermost posterior canal produces a nystagmus identical to that observed in BPV (Table 3)[22(p51)]; in patients with BPV, otoliths have been found in the posterior semicircular canal[23,24]; and patients with disabling BPV are cured after plugging or neurectomy of the posterior canal.[9,25]

Patients with vestibular neuronitis experience abrupt sustained vertigo lasting one to seven days, associated in 25% to 50% with a recent febrile illness that is usually diagnosed as a respiratory tract virus.[12,26] Examination reveals decreased caloric responses in the affected ear and a spontaneous rotatory nystagmus.[12,26,27] The term "vestibular neuronitis" is preferred to the more traditional "labyrinthitis" because hearing loss and tinnitus are absent (the labyrinth includes both the vestibular and cochlear organs).

In patients who unexpectedly died soon after an episode of vestibular neuronitis, pathologic studies of the affected ear demonstrated atrophy of the vestibular nerve with normal sensory organs and blood supply.[28] The observation of identical findings in a patient with herpes zoster oticus and vertigo, together with the frequently observed fever in vestibular neuronitis, has led to the suspi-

TABLE 2.—*Distinguishing Benign From Central Positional Vertigo*

Feature	Benign Pasitianal Vertiga	Central Pasitianal Vertiga
Latent period*	Yes, 2-20 seconds	No
Adaptation†	Yes, lasts <50 seconds	No, nystagmus persists
Fatigability‡	Yes, disappears on repetition	No, persists

*Is there a pause between assuming the supine position and the appearance of vertigo or nystagmus?
†Does the central nervous system *adapt* and extinguish the nystagmus?
‡Does prompt repetiition of the maneuver result in weaker and briefer nystagmus?

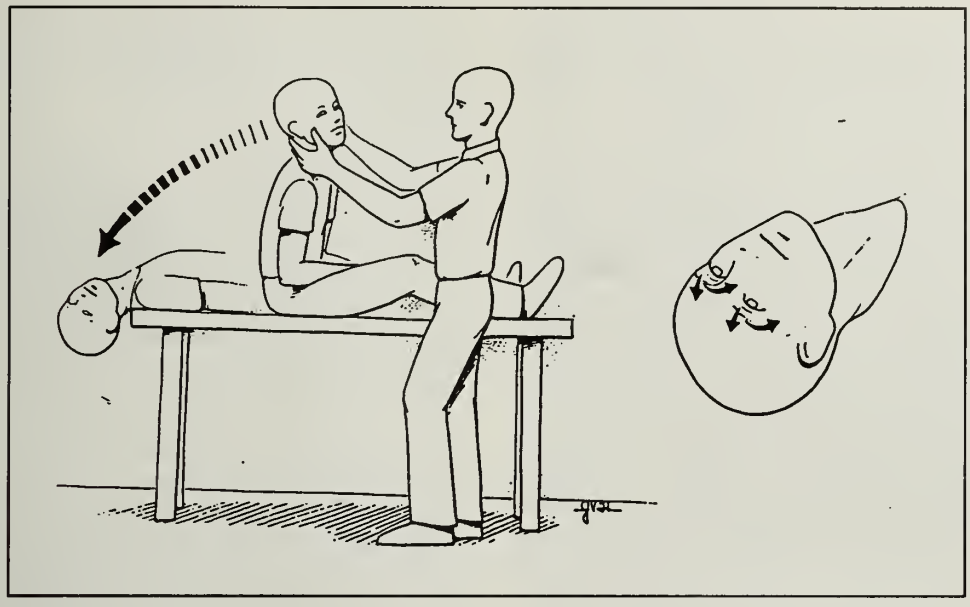

Figure 1.—The Hallpike-Dix maneuver: With the patient seated, the examiner turns the patient's head to one side and directs the patient to lie down, hyperextending the head over the edge of the table. In a positive test, a temporary vertigo and rotatory nystagmus will occur after several seconds, with the quick component of the superior pole of the eye rotating toward the undermost ear. If the test is negative, the examiner should repeat the test with the head turned to the opposite side (adapted from Mohr[10]). Although often referred to as the "Nylen-Barany" test, the designation "Hallpike-Dix" test is more appropriate. Barany and Nylen described the occurrence of benign positional vertigo in the 1920s, but emphasized that position, not movement, of the head was most important.[11,14-16] In a 1952 paper summarizing the findings of 100 patients with benign positional vertigo, Hallpike and Dix emphasized the importance of movement and specifically described the maneuver used today.[12]

cion, never proved, that vestibular neuronitis results from a viral infection.

Meniere's syndrome is a disorder named after Prosper Menière who was the first to attribute vertigo to diseases of the inner ear.[29] The syndrome is associated with vertigo that lasts hours, and, in contrast to other peripheral vestibular disorders, affected patients have cochlear symptoms—neurosensory hearing loss, tinnitus, and ear fullness. Sounds are distorted and tinny to the affected ear, and given that the opposite ear is usually normal, pure tones may be perceived as two separate notes (diplacusis). The characteristic disorder was identified in 1938 in two patients who died during surgical therapy for Meniere's syndrome: the affected ears revealed a massively distended endolymphatic system (endolymphatic hydrops) with herniated and ruptured endolymphatic membranes.[30]

The rotatory nystagmus that is characteristic of unilateral peripheral vestibular disorders (for example, vestibular neuronitis, Meniere's syndrome) reflects the specific connections between the semicircular canals and eye muscles. During head movements, the normal vestibular system stabilizes the retinal image by moving the eyes exactly opposite the head movement. Without this vestibulo-ocular reflex, it would be impossible to focus on objects when walking, riding, or even breathing. The accuracy and efficiency of this reflex can be easily demonstrated by holding a pencil vertically in front of the face and moving it from side to side through a 10-degree arc, five times per second. The pencil will appear blurred because the retina cannot compensate quickly enough for the shifting image. If the experiment is repeated with the pencil stationary and the head moved back and forth through the same arc and with the same frequency, the pencil will remain sharply defined. The eye movements are identical in the two examples, but only in the second experiment are the semicircular canals being used to keep the pencil in focus.[31]

To maintain this stable retinal image, each semicircular canal is linked to two eye muscles, one on each side, that move both eyes in a plane parallel to the canal and opposite the head movement (Table 3). In patients with unilateral peripheral vestibular disorders, an imbalance between the right and left sides allows three ipsilateral and three contralateral muscles to act as if unopposed. Because the normal actions of most of these muscles (all except the medial and lateral recti) will rotate the eye medially or laterally, the eye movements produced in uni-

TABLE 3.—*Connections Between Semicircular Canals and Eye Muscles*

Semicircular Canal	*Ipsilateral*	*Contralateral*
Anterior	Superior rectus	Inferior oblique
Horizontal	Medial rectus	Lateral rectus
Posterior	Superior oblique	Inferior rectus

*From Baloh and Honrubia.[22]

lateral vestibular disease are complicated and always include rotatory components. Pure horizontal or vertical nystagmus is not characteristic of peripheral vestibular disease and should suggest a central cause.

Central Vestibular Disorders

In a classic paper that tabulated the symptoms of 500 different patients with strokes, dizziness was a rare symptom in anterior circulation disease (internal carotid, middle cerebral, anterior cerebral arteries), but affected 75% to 100% with posterior circulation disease (basilar, anterior and posterior inferior cerebellar, vertebral arteries).[32] In 75% of those with dizziness and posterior circulation disease, the diagnosis of stroke was obvious because the dizziness either accompanied or appeared after other neurologic symptoms. In patients with brain-stem ischemia, the symptoms accompanying dizziness were usually dysarthria, numbness, diplopia, or hemiparesis.[32] Cerebellar ischemia, however, may be more difficult to distinguish from peripheral vestibular disease (such as vestibular neuronitis); the associated neurologic finding that suggests a cerebellar cause may be as subtle as a mild dysarthria, vertical nystagmus, dysmetria in one arm instead of two, or early findings of a posterior fossal mass, such as headache or depressed mental status.[33-35] If the direction of the nystagmus is opposite the direction that the patient falls, some think cerebellar ischemia is more likely than peripheral vestibular disease,[33] although exceptions occur.[34]

In 25% of patients with dizziness and posterior circulation disease, dizziness is the sole initial symptom, although an important note is that the other neurologic clues listed earlier usually appear within six weeks.[32] It was concluded that isolated dizziness persisting longer than six weeks rarely results from cerebrovascular disease. In support of this conclusion, another study of 86 patients with idiopathic episodic vertigo (lasting 5 minutes to 24 hours) found no cases of vertebrobasilar ischemia at 3.5 years' follow-up (83% were better, 10% had Meniere's disease, and 7% had BPV).[36]

Multiple Sensory Deficits

Combinations of visual impairment, neuropathy, and vestibular deficits may deprive patients of just enough sensory information that they begin to experience dizziness. These patients, usually elderly, have no dizziness at rest but feel vague unsteadiness when walking, especially in unfamiliar environments or when executing turns. A useful diagnostic test in the office is to have the patient make several right-angle turns when walking. A patient with multiple sensory deficits may begin to feel dizzy, a sensation immediately relieved by additional proprioceptive information, such as allowing the patient to touch the wall or table.

The Mercury and Gemini astronauts experienced no dizziness during flight, presumably because they were strapped to their seats for the entire voyage. During the Apollo, Spacelab, and Shuttle programs, however, astronauts frequently moved around in the weightless environment, depriving themselves of familiar proprioceptive information and sometimes inducing feelings of disequilibrium. This dizziness would resolve, just as in patients with multiple sensory deficits, after simply touching the cabin wall.[37,38]

Clinical Approach

A careful patient interview elicits the diagnosis in at least 75% of patients.[6,7] Open-ended questions help classify the dizziness as *vertigo*, the sensation of movement in the head, implying peripheral or central vestibular disease; *impending faint* (presyncope), implying hypotension; or *disequilibrium*, unsteadiness not in the head, implying cerebellar or proprioceptive disorders. The complaints of some patients, however (40% in one study), may be too vague or diverse to confine to a single category, despite a clinician's best efforts.[7] In patients with vertigo, helpful distinguishing features are the duration of vertigo (BPV, seconds; Meniere's, hours; vestibular neuronitis, days; vertebrobasilar ischemia, minutes to days), precipitating factors (positional or spontaneous), and associated symptoms (cochlear symptoms, fever, head trauma, other neurologic symptoms). The cause of dizziness may become obvious after a careful review of the patient's exposures (welder's fumes, carbon monoxide, hydrocarbon solvents) and medications (quinine, alcohol, antihypertensives, anticonvulsants, antidepressants, cardiovascular medications).[39-41]

Diseases that affect both inner ears equally, such as streptomycin toxicity, do not cause vertigo, because vertigo requires an imbalance between the right and left sides. Instead, patients with bilateral vestibular disease experience a sensation called "oscillopsia" (inability to focus vision during head movements). When patients lack a functional vestibulo-ocular reflex, their environment appears to bounce around just as a video picture jumps around when the camera is carried on a photographer's shoulder.[42]

The physical examination should focus on a patient's vital signs, ears, heart, and nervous system. Nystagmus that appears only on extreme lateral gaze is not pathologic, as it occurs in 60% of normal people.[43] Nystagmus that occurs when the eyes are closer to the primary eye position is abnormal: rotatory nystagmus suggests peripheral or central vestibular disease, and pure horizontal or vertical nystagmus implies a central cause. A positive Romberg test (pronounced increase in body swaying with eyes closed compared with eyes open) suggests proprioceptive disease, not cerebellar disease as is commonly thought.[44] The Hallpike-Dix maneuver (Figure 1) is indicated in patients with positional vertigo. If the clinician suspects multiple sensory deficits, the patient should be observed while walking and making sudden turns. Although many clinicians think that dizziness aggravated by the hyperventilation maneuver identifies a specific "hyperventilation syndrome,"[5] this maneuver may be less specific than previously thought, with some studies showing that as much as 20% of cases of dizziness from all causes (including peripheral vestibular disorders) worsen during forced hyperventilation.[6,8]

Measuring the blood count and electrolyte levels is appropriate in patients with orthostatic hypotension and as a screen for gastrointestinal bleeding, prerenal azotemia, and adrenal insufficiency. In patients with vertigo accompanied by cochlear symptoms, prompt referral for audiometry will address the possibility of Meniere's syndrome. Other laboratory tests are rarely helpful.[6] Electronystagmograms, though commonly done in research studies, rarely contribute new clinical information. Although 65% of electronystagmograms were abnormal in one study of 75 dizzy patients, the positive findings usually confirmed diagnoses obvious from the history and physical examination alone.[45] Furthermore, the clinical observation of nystagmus is just as accurate as electronystagmography in patients with BPV.[17]

Management

Both anticholinergic (scopolamine) and antihistamine (dimenhydrinate, meclizine) medications are commonly used to treat vertigo (astronauts combine scopolamine with amphetamines), although there are few drug trials that have a double-blind placebo design. In motion-sickness experiments in which more than 16,000 soldiers were enrolled, dimenhydrinate and meclizine were more effective than placebo.[46] In human volunteers subjected to rotational accelerations, both scopolamine and dimenhydrinate prevented postrotational vertigo, nausea, and nystagmus better than placebo.[47,48] There are only two positive double-blind placebo trials in dizzy patients, both of short duration: meclizine and dimenhydrinate were each effective in 50 elderly patients with dizziness of diverse causes,[49] and meclizine was effective in 31 patients with vertigo from various causes.[50] Benzodiazepines were ineffective in the treatment of BPV.[51]

Scopolamine and dimenhydrinate have traditionally been used for motion sickness and meclizine for dizziness, though there is no reason why these medications should not be interchangeable. The peak efficacy of the scopolamine patch does not appear until eight hours after application, making it most useful as a prophylactic medication.[52]

Active exercise will expedite the recovery from vertigo. The central nervous system has a remarkable ability to adapt and extinguish any disequilibrium that results from sensory conflicts between the right and left vestibular systems, between the semicircular canals and otolith organs, or between the vestibular and proprioceptive systems.[53] Such adaptation explains why motion sickness resolves on long voyages, why space sickness diminishes after 48 hours of flight, and why dancers can learn to suppress caloric-induced nystagmus.[54] Adaptation occurs more quickly with active exercise. Squirrel monkeys (*Saimiri sciureus*) subjected to unilateral labyrinthectomy are much less ataxic if exercised daily in rotating cages.[55] Humans who actively exercise also recover much more quickly from the vertigo and nystagmus that develop after unilateral labyrinthectomy.[54,56-58] In one study of 67 patients with BPV, 66 were cured after a week of performing simple exercises several times a day.[59]

The management of patients with Meniere's syndrome has focused on attempts to reduce the distention of the endolymphatic space. One double-blind randomized trial of 26 patients with Meniere's syndrome compared a regimen of hydrochlorothiazide, 25 mg three times a day, with placebo.[60] At one year follow-up, the use of hydrochlorothiazide resulted in a substantial reduction of vertigo and hearing loss (there was no difference in the incidence of tinnitus between the two groups). Betahistine hydrochloride, a histamine H_1-agonist that is generally unavailable, was superior to placebo in two studies.[61,62]

Endolymphatic shunt surgery, despite its theoretical attractiveness, was no more effective than a sham procedure (mastoidectomy); 75% of both treatment groups were improved at three years' follow-up.[63,64] In another study of 123 patients with unilateral Meniere's syndrome, the outcome in patients after an endolymphatic shunt operation was no better than in those who refused an operation—60% of both groups were improved at two years' follow-up.[65] Despite these results, which some dispute,[66] the endolymphatic shunt operation is still preferred by a third of US physicians as the initial operation for Meniere's syndrome.[67] Other surgical procedures, such as vestibular neurectomy and labyrinthectomy, are also carried out for Meniere's syndrome, although none have been subjected to a randomized trial.[68]

Patients with multiple sensory deficits may benefit from measures that provide them more sensory information about their environment, such as cataract extraction, appropriate eyeglass prescription, a night light at home, or physical therapy for learning to use a cane or walker.

Prognosis

The prognosis in patients with dizziness is good, with rates of hospital admission, institutionalization, and death no different from those of age-matched controls.[3,4] With follow-up periods varying from 6 months to 12 years, the dizziness improves or resolves in 75% of patients with Meniere's syndrome,[63-65] 83% of patients with idiopathic vertigo,[36] 98% of patients with BPV,[59] and 90% to 100% of patients with vestibular neuronitis.[26,27]

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Pulmonary Surfactant Therapy

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Surfactant replacement therapy is now an integral part of the care of neonates since several clinical trials of natural surfactant extracts and synthetic preparations have shown efficacy in the treatment of infants with hyaline membrane disease. In these studies, early treatment with exogenous surfactant substantially reduced mortality and the incidence of air leak, although it did not appear to reduce the incidence of other complications, in particular bronchopulmonary dysplasia. Early reports of exogenous surfactant therapy in patients with the adult respiratory distress syndrome, although promising, remain limited in number. More research is needed to improve on current modes of therapy and to investigate the possible role of surfactant in other lung diseases of both newborns and adults.

(Poulain FR, Clements JA: Pulmonary surfactant therapy. West J Med 1995; 162:43-50)

The possible role of surface forces in the lungs was first considered in 1929 by the Swiss scientist Kurt von Neergaard.[1] Two and a half decades later, Pattle[2] and Clements[3] independently demonstrated the existence of surface-active material in the alveoli of animal lungs. Soon after, in 1959, Avery and Mead established the relationship between this surface-active material, lung surfactant, and hyaline membrane disease of human neonates.[4] Since then, a great deal of effort has been devoted to studying the biologic properties of lung surfactant and its potential as a human therapy. The first report of the beneficial use of surfactant therapy in neonates with the respiratory distress syndrome (RDS) was published in 1980.[5] Several ensuing trials demonstrated the efficacy of exogenous surfactant in reducing the mortality and morbidity attributable to RDS. These results led the United States Food and Drug Administration (FDA) to approve the use of surfactants in neonates in 1990.

In this review, we summarize some biologic aspects of pulmonary surfactant, outline conclusions drawn from clinical trials using surfactant preparations in neonates, and discuss some of the questions that remain unanswered.*

Surfactant Composition

Lung surfactant is a complex lipoprotein assembled and secreted into the alveolar spaces by alveolar epithelial type II cells. Its composition, being fairly constant among mammalian species,[6] consists of about 90% lipids and 10% proteins. The main lipid fraction is the saturated lecithin dipalmitoyl phosphatidylcholine (DPPC). Negatively charged phospholipids are present in high proportion (10% to 15%), as is free cholesterol (about 10%). A variety of other phospholipids and neutral lipids make up the remainder of the lipids. Three lipid-associated apolipoproteins have been isolated from lung surfactant and designated SP-A, SP-B, and SP-C.[7] Two of these, SP-B and SP-C, are small hydrophobic proteins that co-isolate with lipids. SP-A, on the other hand, more easily dissociates from lipids and can be solubilized in water.[8] A fourth protein, SP-D, has recently been purified from lung lavage and does not appear to directly interact with lipids.[9] SP-D bears striking structural homology to SP-A, and along with mannose-binding protein and serum conglutinin, belongs to the newly described "collectin" family.[10] This complex lipoprotein has unique functional properties.

Biologic Properties of Lung Surfactant

The primary function of lung surfactant is to lower surface tension at the air-water interface of the lung alveoli, thereby stabilizing lung volume at low transpulmonary pressure. Adsorption of DPPC by itself to the liquid surface is poor,[11] but it is greatly enhanced by surfactant apoproteins.[12]

Attention has recently been directed to the immune properties of surfactant. Apoproteins SP-A and SP-D appear to have specific immune properties. Both proteins bind to bacteria[13,14]; SP-A enhances the

*See also the editorial by R. J. Mason, MD, "Surfactant Replacement Therapy—Room for Improvement," on pages 74-76 of this issue.

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ABBREVIATIONS USED IN TEXT

CPHT = colfosceril palmitate, hexadecanol, and tyloxapol
DPPC = dipalmitoyl phosphatidylcholine
FDA = United States Food and Drug Administration
RDS = respiratory distress syndrome

phagocytosis of bacteria[13] and viruses[15] and promotes the chemotaxis of phagocytic cells.[16]

Other properties of surfactant may include inhibiting pulmonary edema formation[17] and enhancing fluid dispersal[18] and ciliary transport in small airways.[19]

Surfactant Metabolism

The synthesis of lung surfactant appears to be restricted to alveolar epithelial type II cells, although nonciliated bronchiolar cells have been shown in several species to make surfactant apoproteins.[20] Once assembled, the components of surfactant are stored in secretory organelles, lamellar bodies, before their secretion into the alveolar liquid subphase where they undergo structural transformations that lead to the formation of the surface layer (Figure 1). Labeling studies show that surfactant is in a state of continuous flux and that type II cells are capable of regulated endocytosis and recycling of the various surfactant components.[21]

Surfactant Replacement Therapy

Before it was approved by the FDA for human use, exogenous surfactant underwent extensive testing in a great number of well-designed, carefully controlled, and properly randomized clinical studies that have set a standard of scientific excellence and productive collaboration in the neonatal community.

We will briefly describe the preparations that were tested (Table 1). Surfactant-TA (Surfacten, Tokoyo Tanabe, Tokyo, Japan) and beractant (Survanta, Abbott Laboratories, Chicago, Illinois) are made from minced lungs and modified by the addition of phospholipids and fatty acids. Infasurf (Forrest Laboratories, New York, NY) and calf lung surfactant extract are made from calf lung lavage extracts, and SF-RI 1 (Alveofact, Boehringer, Ingelheim, Germany) is from cow lung lavage extracts. Curosurf (Chiesi Pharmaceuticals, Parma, Italy) is derived from minced pig lung extracts. Amniotic fluid surfactant is the only human preparation

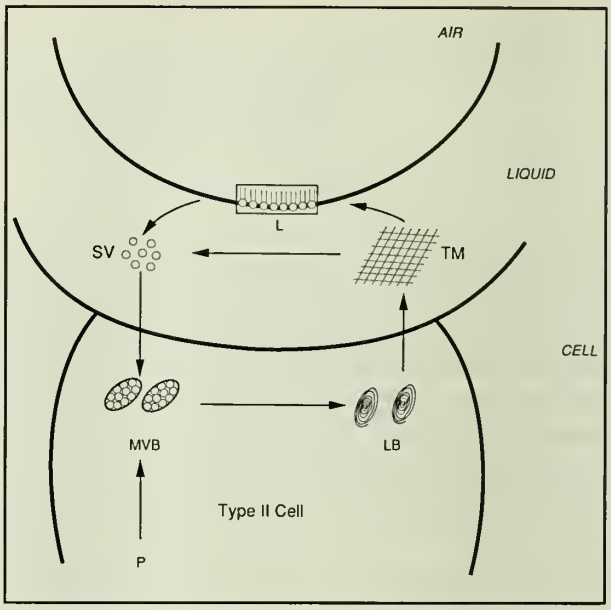

Figure 1.—A simplified overview of surfactant turnover is shown: Type II cells synthesize and assemble precursors **(P)** of surfactant into multivesicular bodies **(MVB)** and secrete lamellar body **(LB)** contents into the alveolar liquid lining where they undergo structural transformations: tubular myelin **(TM)** feeds the surface layer **(L)** and small vesicles **(SV)** are recycled into type II cell multivesicular bodies.

characterized and tested. The two synthetic preparations that were the most extensively tested are the artificial lung-expanding compound (ALEC, Britannia Pharmaceuticals, United Kingdom) and colfosceril palmitate, hexadecanol, and tyloxapol (CPHT; Exosurf Neonatal, Burroughs Wellcome Company, Research Triangle Park, North Carolina), but others were or are being developed.

Analyzing in detail each of the trials is beyond the scope of this review, and our intent is to summarize the conclusions that can be drawn from published results.

Clinical Trials of Exogenous Surfactant in Neonatal Respiratory Distress Syndrome

Trials that followed the report by Fujiwara and colleagues[5] help answer the following questions:

TABLE 1.—*Surfactant Preparations*

Surfactant Type	*Material*	*Proteins*
Bovine	Modified minced lung extracts (surfactant TA [Surfacten])	SP-B, SP-C
Bovine	Modified minced lung extracts (beractant [Survanta])	SP-B, SP-C
Bovine	Calf lung lavage extracts (CLSE, Infasurf)	SP-B, SP-C
Bovine	Cow lung lavage extracts (SF-RI 1 [Alveofact])	SP-B, SP-C
Porcine	Minced lung extracts (Curosurf)	SP-B, SP-C
Human	Human amniotic fluid extract	SP-A, SP-B, SP-C
Synthetic	DPPC-PG (artificial lung-expanding compound)	None
Synthetic	DPPC, CPHT (Exosurf Neonatal)	None

CPHT-colfosceril palmitate, hexadecanol, and tyloxapol; DPPC-PG = dipalmitoylphosphatidylcholine-phosphatidylglycerol; SP-A = surfactant apoprotein A; SP-B = surfactant apoprotein B; SP-C = surfactant apoprotein C

TABLE 2.—*Prophylactic Trials of Surfactant Preparations*

Trial	Preparation	Dosage	Infants: Age, wk (Weight, grams)	Infants: No.	Outcome
Enhorning, et al, 1985[24]	CLSE	Single	< 30	72	↓Death, ↓IVH
Kwong et al, 1985[25]	CLSE	Single	24-28	27	No difference
Kendig et al, 1988[26]	CLSE	Single	25-29	65	↓Pneumothorax
Merritt et al, 1986[27]	Human	Multiple	24-29	60	↓Death, ↓pneumothorax
Soll et al, 1990[28]	Beractant	Single	24-30 (750-1,250)	156	↓Pneumothorax, ↑NEC
Hoekstra et al, 1991[29]	Beractant	Multiple	23-29 (600-1,250)	430	↓Death, ↓pneumothorax
Ten Centre Study Group, 1987[30]	ALEC	Multiple	25-29	328	↓Death
Morley et al, 1988[31]	ALEC	Multiple	< 34	341	↓Death, ↓BPD, ↓IVH in <30 wk
Phibbs et al, 1991[32]	CPHT	Single	(700-1,350)	74	No difference
Bose et al, 1990[33]	CPHT	Single	(700-1,350)	385	↓PIE
Stevenson et al, 1992[34]	CPHT	Single	(500-699)	215	↓Pneumothorax, ↑pulmonary hemorrhage
Corbet et al, 1991[35]	CPHT	Single	(700-1,100)	446	↓Death, ↓pneumothorax

ALEC = artificial lung-expanding compound; BPD = bronchopulmonary dysplasia; CLSE = calf lung surfactant extract; CPHT = colfosceril palmitate, hexadecanol, and tyloxapol; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PIE = pulmonary interstitial emphysema

• *Can the prophylactic administration of exogenous surfactant prevent RDS and its complications?*

The prophylactic administration of surfactant aims at instituting surfactant in the airway as soon as the infant is delivered and before breathing has even begun. Possible advantages of this approach are indicated by experiments in prematurely delivered animals that showed that exogenous materials distribute better when instilled in a partially or totally fluid-filled airway[22] and that, in the absence of surfactant, damage to the airway occurs early (in the first hour) after the initiation of mechanical ventilation.[23] Results from trials testing different preparations (Table 2)[24-35] were subjected to meta-analyses.[36,37]

From these analyses, it was concluded that the prophylactic administration of surfactant decreases neonatal mortality and the incidence of air leak. Although these effects did not reach statistical significance in all trials, they appeared consistent across populations and with all surfactant preparations tested. Despite initial hopes to the contrary, however, the incidence of bronchopulmonary dysplasia, intraventricular hemorrhage, and other complications of prematurity remained essentially unchanged. Because systematic prophylactic treatment of neonates at risk for RDS would result in a large number of them being subjected to unnecessary treatment, investigators were led to test exogenous surfactant therapy in infants with established RDS.

• *Can surfactant therapy decrease the incidence and severity of RDS and its complications?*

In the "rescue" mode of surfactant therapy (also referred to as "treatment"), infants are treated after the diagnosis of RDS has been established by clinical and radiologic criteria. Several investigators tested this approach in randomized trials (Table 3).[38-49] Again, meta-analyses of the results showed a decrease in mortality and air leak similar to that found in prophylactic trials.[36,37] Moreover, there was again little or no effect of surfactant therapy on sequelae associated with RDS. In particular, there was no notable effect on the incidence of bronchopulmonary dysplasia in survivors, although there was variability in the results among different-weight groups within and between studies. Direct comparative trials of the two approaches (prophylactic versus rescue) were also done.

• *Is prophylactic better or worse than rescue therapy in decreasing mortality and morbidity associated with RDS?*

Despite published results from five comparative human trials addressing this question (Table 4),[50-54] the answer remains uncertain. Two trials found no significant differences between the two modes of administration.[53,54] One study found increased oxygen requirement at 28 days after birth in the prophylactic group in contrast with decreased oxygen requirement at 36 weeks postconception in the rescue group.[50] On the contrary, a pronounced decrease in mortality and air leak was found in the group born at or before 26 weeks' gestation that received prophylactic therapy.[51] It was also found that prophylactic therapy decreased mortality when compared with rescue administration in the population of infants (29 to 32 weeks' gestation) studied.[52]

Although prophylactic treatment may lead to a delay in stabilizing a neonate, rescue treatment can be given as soon as the diagnosis of RDS is established, earlier than at the times tested in trials. The OSIRIS trial found a decreased incidence of "death or oxygen dependence at the expected date of delivery" and of air leak in infants treated early, before 2 hours of age, when compared with those treated later,[55] and a recent report from Japan found a decreased incidence of bronchopulmonary dysplasia in infants treated before 30 minutes of age compared with those treated at 6 hours of age.[56]

• *Do additional doses of surfactant provide further benefits to patients?*

Two trials showed benefit from repeated doses,[57,58] although the effects on mortality and the incidence of air

TABLE 3.—*Surfactant "Rescue" Trials*

Trial	Preparation	Dosage	Infant Features: Weight, grams	No.	Lung Physiology	Hours After Birth	Outcome
Gitlin et al, 1987[38]	Surfactant TA	Single	1,000-1,500	41	Fio_2 >0.4	<8	↓Pneumothorax
Raju et al, 1987[39]	Surfactant TA	Single	751-1,750	30	Fio_2 >0.5	<6	↓Death and ↓pneumothorax;↑PDA
Fujiwara et al, 1990[40]	Surfactant TA	Single	750-1,750	100	Fio_2 >0.4		↓Pneumothorax, ↓IVH
Hallman et al, 1985[41]	Human	Multiple	<1,500	45	Fio_2>0.6	<10	↓Pneumothorax
Lang et al, 1990[42]	Human	Multiple	24-32*; 1,500	59	Fio_2 >0.8	<12	↓Pneumothorax
Horbar et al, 1989[43]	Beractant	Single	750-1,750	159	Fio_2 >0.4	3-6	↓Pneumothorax
Horbar et al, 1990[44]	Beractant	Single	750-1,750	106	Fio_2 >0.4	3-6	↑IVH
Liechty et al, 1991[45]	Beractant	Multiple	600-1,750	798	Fio_2 >0.4	<8	↓Death, ↓pneumothorax
Gortner et al, 1990[46]	SF-RI 1	Multiple	25-30*	69		<1	No difference
European Collaborative Group, 1988[47]	Porcine	Single	700-2,000	146	Fio_2 >0.6	2-15	↓Death, ↓pneumothorax
Phibbs et al, 1991[32]	CPHT	Single	>650	104	Fio_2 >0.4-0.5	4-24	No difference
Long et al, 1991[48]	CPHT	Multiple	700-1,350	419	a/A <0.22	2-24	↓Death, ↓pneumothorax and PIE
Long et al, 1991[49]	CPHT	Multiple	>1,250	1,237	a/A <0.22	2-24	↓Death; ↓BPD and pneumothorax; ↓IVH and ↓PDA

a/A = arterial-alveolar Po_2 ratio; BPD = bronchopulmonary dysplasia; CPHT = colfosceril palmitate, hexadecanol, and tyloxapol; Fio_2 = fraction of inspired oxygen; IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; PIE = pulmonary interstitial emphysema

*Age in weeks.

leak reached significance only in the larger study.[58] It was reported in one abstract that infants treated with multiple doses of the synthetic surfactant CPHT had reduced neonatal mortality and a reduced need for oxygen and ventilatory support.[59] A later report of a large, albeit not placebo-controlled or blinded, international study indicated that more than two doses of CPHT appear to provide little, if any, additional benefit.[55]

• *Is surfactant instillation safe?*

The most common adverse reaction seen after the tracheal instillation of surfactant was a transient deterioration of gas exchange, which responded well to and often could be prevented by an adjustment of the ventilator settings.[60,61] Airway obstruction occurred with an incidence of about 3 patients per 1,000 in trials testing the use of CPHT.[62] The incidence of such events when using other surfactant preparations has not been precisely ascertained.

An increase in the incidence of pulmonary hemorrhage was reported in a trial examining the effects of prophylactic CPHT in infants weighing 500 to 699 grams at birth.[34] On review of retrospective[63,64] and autopsy analyses,[65] however, the relative risk for pulmonary hemorrhage with any surfactant therapy is estimated to be no greater than 1.5.[64]

A report of an increase in the incidence of intraventricular hemorrhage in treated infants[44] was not confirmed by other trials and appears to have been an isolated incidence.[66]

Administering human or animal-derived extracts to infants raised concerns over the infectious risk posed to patients and the potential for their sensitization to the protein fraction contained in the preparations. Isolated reports of increased incidence of bacterial sepsis did not reach statistical significance,[29] and to date no other report of serious infectious complication has appeared. Two studies failed to detect immune complexes[67] or circulating antibodies[68] in the serum of infants who received natural preparations, but one showed a suppression of the mitogen-induced proliferation of cord blood lymphocytes by the natural surfactant SF-RI 1.[68]

Although the long-term follow-up of infants treated with surfactants has been limited both in the number of subjects and the duration, it has not shown adverse developmental effects of treatment.[69-74] Increased survival of infants with disabilities might be expected, however, and several studies indicated such a trend.[69,71,72]

• *Are any of the available preparations better than the others?*

There is currently one published trial comparing the efficacy of CPHT and beractant administered in a rescue mode.[75] Although there were small differences favoring the use of beractant in the effects on ventilatory settings needed to maintain comparable early gas exchange in the two groups, there was no observed difference in the mortality or incidence of any of the complications between the two groups. Studies comparing different preparations with those already tested are ongoing, but results have yet to be published.

Surfactant Therapy for Other Pulmonary Diseases

The main measurable effect of exogenous surfactant on lung mechanics of infants with RDS is an increase in functional residual capacity, possibly through stabilizing partially ventilated alveolar units and recruiting previ-

TABLE 4.—*Rescue Versus Prophylaxis Comparative Trials*

Trial	Preparation	Dosage	Infants			Outcome
			Age, wk	No.	Lung Physiology	
Dunn et al, 1991[50]	CLSE	Multiple	< 30	182	<6 hr*	↓Pneumothorax and ↓BPD in treatment group
Kendig et al, 1991[51]	CLSE	Multiple	24-29	479	FiO_2 >0.4	↓Death and ↓pneumothorax in prophylaxis group
Kattwinkel et al, 1993[52]	CLSE	Multiple	29-32	1,398	FiO_2 >0.3	↓Death in prophylaxis group
Merritt et al, 1991[53]	Human	Multiple	24-29	203	FiO_2 >0.5; 2-12 hr*	No difference
Egberts et al, 1993[54]	Porcine	Multiple	26-29	147	FiO_2 >0.6; 6-24 hr*	No difference

BPD = bronchopulmonary dysplasia, CLSE = calf lung surfactant extract, FiO_2 = fraction of inspired oxygen

*Hours refer to time after birth.

ously nonventilated ones.[76] Tidal volume and lung compliance, however, remain unchanged or decrease slightly.[76]

Diseases of the lungs other than RDS may also be ameliorated with surfactant therapy. Studies in animals have suggested benefits of using exogenous surfactant in a variety of conditions, including pneumonia (bacterial,[77] aspiration[78]), asthma,[79] and after lung transplantation.[80] In humans, exogenous surfactant improved lung mechanics and gas exchange in neonates with the meconium aspiration syndrome[81] and in infants with respiratory failure requiring extracorporeal membrane oxygenation.[82] The use of surfactant replacement therapy was also tested in adults and children with adult RDS. Preliminary reports have been encouraging,[83,84] but controlled trials are clearly called for.

Remaining Questions, Future Prospects

Despite the success of surfactant replacement therapy in neonates with RDS, several questions pertaining to its use in clinical practice remain unanswered. In most trials a small fraction of the infants had little or no response to therapy.[85,86] The proportion of these "nonresponders" varied with the population studied, but was as high as 24% in one study.[86] Subsequent analyses suggested that the presence of prenatal asphyxia increases the risk of a poor response,[87] as do those of large patent ductus arteriosus and high fluid intake.[88] A number of other factors could also contribute to limit the response to surfactant therapy:

- The dose of surfactant administered may be insufficient. The amount of surfactant administered in trials varied from 60 to 200 mg of phospholipids per kilogram. These doses were chosen largely on the basis of theoretical considerations, but little experimental work has been done to establish the correct dosing and administration regimen. Two trials specifically addressed the effects of the initial dosage. One found that administering 120 mg per kg of surfactant TA was more effective than half that dose.[89] Another showed that 67.5 mg per kg of CPHT was more effective than half and as effective as double that dose.[90]
- The administration of surfactant may be ineffective because surfactant fails to reach the respiratory units or it is inactivated in situ, for instance by extravasated serum proteins.[91] The distribution of exogenous surfactant in the lungs may also be affected by its mode of delivery, that is, bolus versus slow instillation.[92] Aerosol delivery of surfactants is being tested in the treatment of patients with adult RDS,[84] but it has the serious disadvantage that, with current methods, administering an adequate dose takes hours or even days.
- Ventilation strategies may affect the response to therapy.[88] Preparations with different physical characteristics are expected to affect the patient's lung mechanics differently,[76] and ventilator settings may need to be adjusted accordingly, as has been shown in animals.[93]
- Surfactant therapy is only a palliative treatment, limited in time, and patients ultimately depend on an effective endogenous surfactant production for full recovery. This point is illustrated by the report of a patient who died of neonatal RDS refractory to repeated exogenous surfactant administration and who was found at autopsy to lack the normal production of surfactant apoprotein B because of a genetic defect.[94,95] Other genetic abnormalities are likely to be discovered that alter the normal production or functional properties of surfactant components.
- The administration of antenatal steroids is an important element in determining outcome in infants, as shown by several investigators. One report showed recently that infants whose mothers had received steroids antenatally had lower requirements for surfactant treatment or ventilator support and a lower incidence of intraventricular hemorrhage.[96] A retrospective analysis of trials using beractant showed that the prenatal administration of steroids reduced neonatal mortality to the same extent as did the postnatal administration of surfactant and that steroids and surfactant together have additive effects.[97] These observations confirm the results of an earlier analysis[98] and of animal experiments showing structural maturation of the lung after prenatal steroid therapy.[99]

Finally, several laboratories are working to improve currently available preparations. The use of recombinant and synthetic peptides that attempt to mimic the proper-

ties of hydrophobic surfactant-associated proteins is a promising avenue of approach.[100-102]

Conclusions

In early 1995, have the closing lines in the fascinating story of surfactant biology been written? To the contrary, several important questions remain about pulmonary surfactant, its biologic processes, and its role in lung homeostasis and disease states. Furthermore, investigation of other modes of therapy, such as partial[103] or total[104] liquid ventilation, could lead to alternative treatments for special situations in which exogenous surfactant may prove not to be optimal therapy. Although we should not underestimate the achievements of recent years in this field, it is clear that much more research will be needed to complete our understanding of the lung surfactant system and to enable us to manipulate it to best advantage for patients with pulmonary diseases.

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Epitomes

Important Advances in Clinical Medicine

Anesthesiology

Stephen H. Jackson, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association, and the summaries were prepared under the direction of Dr Jackson and the panel.

New Muscle Relaxants

FOUR NEW MUSCLE RELAXANTS have recently been introduced into clinical practice. These muscle relaxants must be considered in comparison with atracurium besylate and vecuronium bromide, two effective drugs that have an intermediate duration of action, little cardiovascular effect, and a low incidence of postoperative residual weakness. Pipecuronium bromide and doxacurium chloride have a long duration of action, similar to tubocurarine chloride and pancuronium bromide, but without their cardiovascular effects of hypotension and tachycardia, respectively. The cardiovascular safety is excellent, but no better than that of vecuronium. The difficulty of rapidly antagonizing neuromuscular block produced by pipecuronium and doxacurium with consequent persistent postoperative weakness makes them less cost-effective than the intermediate-duration drugs for most surgical situations. Their long duration of action may be of value during long operations, where patients' tracheas will remain intubated postoperatively, or in intensive care units.

Mivacurium chloride is the only short-acting, nondepolarizing muscle relaxant, as it is hydrolyzed by plasma cholinesterase. Intubating doses can stimulate histamine release and, in doses of 0.2 mg per kg or more, may produce hypotension with an incidence similar to that of atracurium. Neuromuscular function following intubating doses begins to recover in 10 to 15 minutes. For procedures longer than 30 minutes, mivacurium is best administered by infusion. A guideline for infusion is to start at a rate of 10 μg per kg per minute as soon as there is evidence of recovery from the initial intubating dose, then titrate the infusion rate to the subsequent neuromuscular response. Neuromuscular recovery is rapid even after an infusion of several hours. Full spontaneous recovery after an infusion takes 15 to 20 minutes, and this time is halved by the administration of neostigmine bromide. Mivacurium's duration is substantially prolonged in patients with diminished plasma cholinesterase activity. Its duration is increased by 50% in patients with renal failure and by a factor of 3 in those with severe liver disease. Patients homozygous for the atypical cholinesterase enzyme may be paralyzed for several hours. There is no evidence that patient care is enhanced by using mivacurium versus the intermediate-duration drugs vecuronium or atracurium.

The fourth new drug is rocuronium bromide, which has an intermediate duration of action and minimal cardiovascular effects. The pharmacologic advantage of rocuronium is its rapid onset of action. It is the first nondepolarizing muscle relaxant to have an onset that approaches that of succinylcholine chloride. In doses of 0.6 to 0.9 mg per kg, it produces paralysis in 60 to 90 seconds. Its onset is about 50% slower than that of succinylcholine, but intubating conditions at 60 to 90 seconds are similar for both drugs; therefore, rocuronium may be useful for rapid-sequence tracheal intubation. This drug is not a complete replacement for succinylcholine, however, as it does not have an ultrashort duration of action. Rocuronium is priced competitively with vecuronium and atracurium.

The clinical roles of rocuronium and mivacurium have been expanded by a recent notice by the United States Food and Drug Administration (FDA) on succinylcholine's potential to produce sudden, unexpected, hyperkalemic cardiac arrest in children with undiagnosed muscular dystrophy. The FDA has determined that "except when used for emergency tracheal intubation or in instances where immediate securing of the airway is necessary, succinylcholine is contraindicated in pediatric patients." This statement is under review, however, and the contraindication will be revised to a warning. Nonetheless, clinicians who have routinely used succinylcholine to facilitate straightforward elective tracheal intubation in children have been advised to find an alternative. If rapid onset is desired, then rocuronium is an acceptable alternative. If brief duration is paramount, then

mivacurium may be acceptable. Neither drug can be considered a full replacement for succinylcholine, however.

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Preparing Children for Anesthesia and Surgery

In preparing a child for surgery, an anesthesiologist is faced with the unenviable task of separating a starved and frightened child from anxious parents. The scientific rationale for a lengthy preoperative fast has recently been questioned, and based on new studies, preoperative fasting guidelines have been modified. In addition, newer hypnotic drugs and modes of administration can ease the separation of children from their parents.

Whereas the tradition of a preoperative fast can be traced to 1858, decades of studying the epidemiology and risk factors for perianesthetic aspiration of stomach contents have not determined the proper duration of the fast. It has now been established that the gastric fluid of children (older than 1 year) who are allowed to drink clear liquids up until two hours before anesthesia is no greater in acidity or volume than that of children who fast overnight. Therefore, ingesting clear liquids up to two hours before an operation does not appear to increase anesthetic risk. Because substantial physiologic benefit from a shortened fast has not yet been demonstrated, children with esophageal or gastric disease, severe neurologic disease, suffering from pain, receiving narcotics, or presenting airway management difficulties would be likely to benefit from more conservative fasting guidelines. In addition, until more data become available, infants younger than 1 year should fast for three to four hours before a surgical procedure.

The "shot to calm you" is understandably unpopular with children and parents alike. Oral, rectal, or nasal administration of the water-soluble benzodiazepine midazolam hydrochloride is an effective and painless alternative to intramuscular administration. Sedative doses of midazolam when given by these routes range between 0.5 and 1.0 mg per kg. About half of the drug is bioavailable following oral or rectal administration, and the maximal sedative effect will occur within 20 to 30 minutes. Administering the drug nasally increases bioavailability (to about 75%) and provides an even more rapid onset. Because the effects generally dissipate within an hour, recovery from anesthesia is not appreciably prolonged. Oral ketamine hydrochloride, 5 to 10 mg per kg, can be substituted for midazolam; some children may experience unpleasant psychomimetic effects, however, and recovery may be prolonged.

An oral transmucosal form of fentanyl citrate (Oralet) is now available. This consists of a medicated lozenge on a plastic holder. The dose of fentanyl (200 to 400 μg) in each Oralet is substantial, mandating strict adherence to administration and monitoring precautions.

In recent years the preoperative preparation of children for anesthesia and surgery has been reevaluated. Less stringent preoperative fasting guidelines and improvements in preoperative medication techniques have resulted in a less traumatic anesthetic experience without compromising safety.

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Inhaled Nitric Oxide

Treatment of pulmonary hypertension with intravenous vasodilators is limited by systemic hypotension (due to the systemic vasodilator effects of all pulmonary vasodilators) and hypoxemia (due to the reversal of hypoxic pulmonary vasoconstriction). Inhaled nitric oxide (NO) now appears to be a major advance in the therapy for pulmonary hypertension.

Vascular endothelium is able to modulate vascular tone by producing substances that dilate the adjacent smooth muscle. In 1987 NO was identified as endothelium-derived relaxing factor. Nitric oxide produced by the endothelium diffuses into vascular smooth muscle, where it activates soluble guanylate cyclase; the subsequent increase in levels of intracellular cyclic guanine monophosphate produces smooth muscle vasodilation. Endothelium-independent nitrovasodilators such as nitroglycerin and sodium nitroprusside also activate guanylate cyclase, but do so by directly releasing NO. They release NO into both the pulmonary and systemic circulations, so that systemic vasodilation accompanies the pulmonary vasodilation. Nitric oxide itself is rapidly inactivated by hemoglobin in blood, so that the effect of inhaled NO may be localized to the lungs. Thus, inhaled NO diffuses from the alveoli to pulmonary vascular muscle and produces pulmonary vasodilation but no systemic effects. Although NO as a component of air pollution has been considered a toxic gas, it has relatively low toxicity; nitrogen oxides such as nitrogen dioxide that form from NO over time are polluting toxic compounds.

In animals, inhaled NO (5 to 80 parts per million) reverses pulmonary hypertension produced by global hypoxia, thromboxane-mimetic infusion, or heparin-protamine interactions. The pulmonary vasodilation is rapid, completely reversible, and selective, with no

systemic vasodilation or other adverse effects. Studies in human volunteers have shown that inhaled NO reversed pulmonary hypertension caused by breathing a hypoxic gas mixture (12% oxygen). The effects of inhaled NO occurred within the first minute of inhalation, and there were no systemic effects.

Inhaled NO (40 ppm) has now been shown to be an effective, selective pulmonary vasodilator in the treatment of acute pulmonary hypertension. In contrast, epoprostenol (formerly prostacyclin) produces dose-related reductions in both pulmonary and systemic vascular resistance. The effects of inhaled NO are fully reversible within five minutes of discontinuation and can be reproduced with repeated administration. Inhaled NO has selectively decreased pulmonary arterial pressure and pulmonary vascular resistance in patients with congenital heart disease and after cardiac surgery. Inhaled NO improves oxygenation in newborns with persistent pulmonary hypertension, presumably by decreasing shunting across a patent foramen ovale or ductus arteriosus.

Inhaled NO has now become a therapeutic option in patients with severe adult respiratory distress syndrome (ARDS). Pulmonary hypertension and hypoxemia universally occur in patients with ARDS; the severity of each relates to mortality. Intravenous pulmonary vasodilator therapy with agents such as nitroglycerin sodium, nitroprusside, alprostadil (prostaglandin E), epoprostenol, and nifedipine results in small decreases in pulmonary arterial pressure but large decreases in systemic blood pressure and arterial oxygenation. The adverse effects on oxygenation occur because the decrease in pulmonary vascular resistance is primarily due to the reversal of hypoxic pulmonary vasoconstriction. In patients with ARDS, inhaled NO can decrease pulmonary vascular resistance and improve oxygenation. The improvement in oxygenation occurs because inhaled NO (as opposed to intravenous vasodilators) is distributed according to ventilation so that the associated vasodilation increases blood flow to well-ventilated alveoli. The magnitude of improvement in pulmonary hypertension and oxygenation is directly related to the degree of abnormality in each. Nitric oxide concentrations of 0.3 to 4.0 ppm are effective, and beneficial effects are sustained during administration periods as long as two months for patients on ventilators.

Although inhaled NO is clearly effective in improving pulmonary hemodynamics and oxygenation, the role of inhaled NO in patients with ARDS requires additional study. By ameliorating pulmonary hypertension and hypoxemia, inhaled NO may decrease the incidence of pulmonary edema, oxygen toxicity, and pulmonary barotrauma, thereby allowing the lungs to heal. The effects of nitric oxide and nitrogen dioxide on repair or fibrosis in injured lungs and on pulmonary host defenses are largely unknown, however. Survival with prolonged administration of inhaled NO was 86% in one major study, but only 14% in another major study. Inhaled NO is currently used by many centers on a "compassionate use" basis for patients with severe hypoxemia, but controlled clinical trials are needed to determine its value in most patients with ARDS.

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Operative Hysteroscopy Intravascular Absorption Syndrome

ANESTHESIOLOGISTS ROUTINELY anticipate, recognize, and treat volume and electrolyte disturbances during transurethral resection of the prostate (TURP syndrome), but it is now established that operative hysteroscopy has the same potential for these serious pathophysiologic changes. The absorbed volume of fluids employed for uterine distention depends on the extent of intrauterine transection of vascular beds, the intrauterine distention pressures, the volume of media used, and the duration of the procedure. The biochemical composition of the instilled fluids determines the physiologic alterations.

Menstruant women have been shown to be at high risk for death or brain damage from even modest hyponatremia and, perhaps even more important, hypoosmolemia. The earliest signs of this syndrome are confusion and bradycardia with systolic and diastolic hypertension. As with the TURP syndrome, it may be advantageous to use regional anesthesia because awake patients are likely to display precursor symptoms that portend impending brain or cardiac dysfunction and injury. For patients subjected to general anesthesia, delayed diagnosis of the syndrome of operative hysteroscopy intravascular absorption (OHIA) can be mitigated against by adhering to a predetermined schedule for sampling patient blood for rapidly measuring the serum sodium concentration. An instillate solution that contains ethanol 1% as a biologic marker can be used to estimate fluid absorption by measuring the end-tidal ethanol content.

Dextran 70 32% in a 10% solution of glucose (Hyskon) is a hyperosmolar, viscous fluid (molecular weight 70,000) that is immiscible in blood and slowly metabolized over several days. It increases plasma oncotic pressure to the extent that it expands blood volume by ten times its absorbed volume. When substantial volumes (> 500 ml) are absorbed, hypervolemic pulmonary edema is to be expected; serum osmolarity and sodium changes are less prominent. Therefore, the use of Hyskon demands meticulous measurement of the instilled volume and a preoperative agreement with the surgeon as to the maximal acceptable volume instilled before the hysteroscopy is stopped. A prominent sign of intravascular overload is decreasing arterial oxygen saturation. Moreover, intravas-

cular overload may first become manifest during emergence from anesthesia when the vasodilatory effects of anesthetic drugs and techniques are dissipated or positive pressure ventilation is discontinued. Hyskon may directly cause a coagulopathy.

Both 1.5% glycine and a premixture of 2.7% sorbitol and 0.54% mannitol are low-viscosity, hypo-osmolar (200 and 178 mOsm per liter, respectively), rapidly metabolized instilling fluids. Excessive absorption can result in substantial hyponatremia and hypo-osmolemia.

A solution of 5% mannitol may have a wider margin of safety compared with the other instilling fluids because it is iso-osmolar (278 mOsm per liter). In fact, mannitol is commonly administered intravenously during neuroanesthesia, often in volumes and concentrations greater than those encountered in operative hysteroscopy and without pathophysiologic sequelae. Excessive intravascular absorption of instilled 5% mannitol solution will cause hyponatremia, but serum osmolarity will not change. Furthermore, mannitol initiates a diuresis that self-corrects volume overload.

Although treatment regimens for hyponatremia, hypo-osmolemia, and circulatory overload are well established, anesthetic management of these otherwise healthy women should emphasize the prevention of the OHIA syndrome and its attendant morbidity and possible mortality.

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Desflurane—A New Inhalation Anesthetic

BEFORE 1993, three volatile inhalation anesthetics were in routine use. These inhalation anesthetics—halothane, enflurane, and isoflurane—have many desirable qualities. As the number of outpatient procedures continues to increase, recent emphasis in anesthetic practice has been toward the development of agents that provide more rapid recovery. A new inhalation anesthetic, desflurane, provides more precise control during delivery and more rapid recovery than preexisting inhalation anesthetics. These improved properties result from its low blood-gas solubility coefficient, which promotes more rapid induction and emergence from anesthesia. This blood-gas solubility coefficient is 0.45, which is similar to cyclopropane (0.42) and nitrous oxide (0.47) and less than half that of isoflurane (1.4). Sevoflurane is another new inhalational agent that has a low solubility coefficient (0.60), but it is still undergoing clinical trials for approval by the Food and Drug Administration.

Desflurane was recently released for clinical use in the United States. Because its high vapor pressure at 20°C is 669 mm of mercury, desflurane is near its boiling point at room temperature. Accurate delivery must be accomplished by using a heated vaporizer that maintains its near-constant temperature, converting desflurane to a gas and then blending this gas with fresh gas flow. In addition to its lower blood-gas solubility, another of desflurane's attractive properties is its low level of biotransformation in the body. Many of the toxicities attributed to earlier inhalation anesthetics are caused by metabolites from hepatic biotransformation. Desflurane is biotransformed at less than an eighth the rate of isoflurane, which previously had been the least biotransformed inhalation agent. In addition, it has excellent physical stability. Its effect on vital organ systems, when higher concentrations are used, is similar to that of existing inhalation agents. It depresses ventilation, lowers mean arterial pressure, and causes some cerebral vasodilation.

Desflurane differs from sevoflurane in several ways: it is stable in carbon dioxide absorbents where sevoflurane has some instability, it undergoes much less hepatic biotransformation than sevoflurane, it may produce a tachycardia at higher concentrations, and its pungency produces airway irritation that precludes its use for inhalation inductions in children.

Desflurane should not produce hepatotoxicity of the form observed with halothane. Although it is not perfect, it does appear to offer specific advantages over previous agents. Cost-benefit comparisons with existing inhalational agents will be another important consideration.

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Intraspinal Narcotics for Obstetric Analgesia

THE USE OF intraspinal narcotics has found widespread acceptance in obstetric analgesia, but has generally been confined to epidural administration. A better understanding of the pharmacology of narcotics and advances in the equipment available have led to the increasing use of intrathecal narcotics in labor. This technique is now a reasonable alternative for women in early labor, in particular, and perhaps a cost-effective alternative in obstetric centers without full-time "in-house" obstetric anesthesia services.

The early use of intrathecal morphine sulfate for labor was effective, but the side effects of pruritus, nausea, and vomiting and the limitations of a single injection (that is, no easy route for further intervention) and its slow onset (30 to 90 minutes) led to its near abandonment. The technique was recently "reinvented," however. The problem of a slow onset was solved by adding one of the lipid-

soluble narcotics, fentanyl citrate (25 μg) or sufentanil citrate (10 μg), to intrathecal morphine (0.1 to 0.3 mg). The lipid-soluble narcotic rapidly penetrates neural tissue, and thus, analgesia is achieved within minutes, allowing morphine to become effective later. The lipid-soluble narcotics provide brief (60 to 90 minute) analgesia, whereas the morphine may provide hours of pain relief. A second advancement was the introduction of both a combined spinal-epidural technique and long pencil-point spinal needles. Using the latter produces a low incidence of postdural puncture headaches (< 1%). The needles can be passed through a standard epidural needle, thus allowing the administration of intrathecal narcotics—morphine, fentanyl, or sufentanil, and possibly small doses of lidocaine or bupivacaine hydrochloride—before placing an epidural catheter. The catheter can then be used for further labor analgesia as needed or for a surgical delivery with concentrated local anesthetics, given epidurally, if indicated.

The use of the combined spinal-epidural technique has been particularly helpful for patients in early labor or for those seeking a more natural delivery—that is, some analgesia but full or greater motor control. This technique has even permitted women to ambulate during labor and is commonly referred to as a "walking epidural." It may also be useful in small community hospitals unable to provide 24-hour epidural anesthesia coverage. Intrathecal narcotics can be administered to provide some pain relief and the catheter then used for further labor analgesia or possible surgical intervention.

This technique is not without side effects. Pruritus is common (50%) and must be treated aggressively (using nalbuphine hydrochloride or naloxone hydrochloride) if the patient is to be comfortable. Nausea and vomiting also occur, but to a lesser extent (30%). Mild hypotension and even respiratory depression have also been reported. Further, narcotics alone provide only analgesia, which may not be sufficient pain relief for many women in active labor who will require further intervention, such as epidural analgesia with a local anesthetic. The use of intrathecal narcotics for labor and of the combined spinal-epidural technique has added an important new choice for labor analgesia.

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New Advances in Airway Management

In the past, clinicians faced with patients requiring ventilation had limited options short of tracheotomy: ventilate by mask or intubate by blind nasal intubation or direct laryngoscopy. Inadequate ventilation due to unsuccessful management of a patient's airway has been shown to be the main cause of brain damage or death. The American Society of Anesthesiologists' "difficult airway" algorithm presents a logical progression of alternative airway management techniques after failed intubation.

One of the key issues for managing the airway is having several options available to physicians to handle the many different airway scenarios. Two new and innovative methods can help: laryngeal mask airway and esophageal-tracheal combination tube.

The laryngeal mask airway consists of a conventional plastic tracheal tube in which the distal end has been replaced by a miniature inflatable face mask. It is inserted blindly through the oral cavity so that the distal end, once inflated, forms an oval seal around the laryngeal inlet. It allows for both oxygenation and ventilation. Both medical and paramedical personnel have a higher rate of success in placing the laryngeal mask airway than inserting an endotracheal tube by standard laryngoscopy. The laryngeal mask airway has few contraindications, the most important ones being patients with a full stomach, massive obesity, hiatal hernia, or gastroesophageal paresis.

The esophageal-tracheal combination tube, in contrast to the laryngeal mask, has been approved for use during cardiopulmonary resuscitation both in hospitals and in the field. It consists of a double-lumen tube with two inflatable balloon cuffs. The proximal (or pharyngeal) cuff replaces the face mask of the old esophageal obturator airway. The "esophageal" lumen has a distal blocked end and perforations at the level of the pharynx. The second lumen resembles a conventional endotracheal tube. The combination tube is inserted blindly through the oral cavity, and regardless of whether esophageal or tracheal intubation is accomplished, the physician is able to ventilate the patient using the appropriate proximal lumen. This combination tube also has contraindications, the most important being esophageal disease. In summary, both methods can be life saving and are especially helpful to physicians who rarely do laryngoscopy.

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Alerts, Notices, and Case Reports

Cactus Thorn Embedded in the Cartilaginous Proximal Tibia

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WE DESCRIBE the clinical course of a child with an unrecognized cactus thorn injury to his knee. This report highlights the difficulties of diagnosing and treating such injuries, difficulties that are important to primary care, emergency, and tertiary care physicians. These include the diagnosis of knee pain in children in general and cactus thorn injuries in particular. The consequences of thorn injuries are uncertain, depending on the unusual problems of thorn structure, operative technical challenges, and nonbacterial inflammation sequelae.

Report of a Case

The patient, a 3-year-old boy, was referred with a painful mass on the anteromedial aspect of his knee and a diagnosis of "dislocated meniscus." The child had been in good health until four days before admission when he had the insidious onset of knee pain and no recollection of trauma. His physician had noted a tender lump near the medial joint line with mild swelling of the knee and mild restriction of motion. The patient had no constitutional symptoms of fever, weight loss, or other joint problems.

Additional history revealed that the child had fallen on a cactus seven days before admission, and at that time his father had removed five tiny (approximately 1 mm in length) thorns from the skin around the knee. On physical examination the epidermal thorn penetration sites were barely visible. There was a tender dome-shaped mass 3 cm in diameter over the proximal medial tibia with mild surrounding inflammation and no sign of overlying skin injury or a needle track (Figure 1). The patient had an antalgic gait and pain at the extreme of flexion (110 degrees) but painless full knee extension. McMurray's test was painful but negative for popping. Knee ligaments and tendons were normal. The musculoskeletal examination and the general examination otherwise showed no abnormalities. Plain radiographs at this time were also normal. The diagnosis was unclear, but possible causes of the mass considered were neoplasia, developmental abnormalities, inflammation, and trauma in the tissues of the knee region.

To better evaluate the location and tissue characteristics of the mass, magnetic resonance imaging (MRI) was done (Figure 2), and showed a 4 cm × 1 mm × 1 mm foreign body in the proximal tibial cartilaginous epiphysis extending superficially to the perichondrium. This signal was initially assessed to be an artifact, but on subsequent evaluation was interpreted as a cactus thorn. Also demonstrated in the MRI was a dome of inflammatory reactive tissue overlying the point of entry and corresponding in size to the mass on physical examination. All intraarticular structures including the medial meniscus were normal.

Chickenpox developed, resulting in a low-grade fever (37.8°C [100°F]), and the child was treated with acyclovir. This delayed the operative removal of the thorn, allowing observation of the natural history of this condition for an additional three days. The inflammatory mass increased in size by 10% and tenderness persisted, but there were no signs of infection of the tibia, knee joint, or lymphatics and no worsening of the fever (40°C maximum) or increased erythrocyte sedimentation rate (40 mm per hour maximum) presumably due to the chickenpox infection or a foreign body reaction.

With the patient under general anesthesia, the thorn was removed in the operating room by an incision directly over the center of the domed mass. The age of the child, the size of the thorn, and the possible difficulty in finding it precluded the use of local anesthesia. When the pseudocapsule was incised, the thorn presented itself and was extracted in one piece. The tract was gently debrided, the wound irrigated, and the skin closed. The thorn and debrided tissue were subjected to histologic and microbial analysis. All cultures (including fungal) were negative for pathogens. The incision healed uneventfully, and the swelling subsided over the ensuing six weeks. At two-year follow-up, knee function and appearance were normal by physical and radiographic examinations.

Discussion

This case illustrates the problem of diagnosing knee pain in children and the difficulties associated with cactus thorn injuries. A wide range of diagnostic possibilities should be considered in a child with monoarticular symptoms, including developmental, neoplastic, infectious, inflammatory, and traumatic processes. Foreign body injuries are usually associated with histories of acute injury and apparent wounds, but this is not always the case with cactus thorn injuries.

Cactus thorns have a wide variety of forms and shapes that cause several characteristic clinical problems.[1] Multiple superficial thorns are painful and difficult to remove. Single thorns can be sharper than surgical needles and can penetrate beneath the skin, often leaving minimal tracks and making diagnosis and localization difficult. Many

(Stevens MA, DeCoster TA, Renwick SE: Cactus thorn embedded in the cartilaginous proximal tibia. West J Med 1995; 162:57-59)

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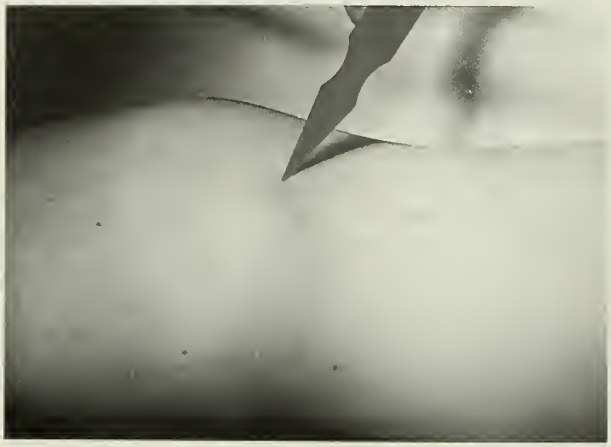

Figure 1.—On the initial presentation, a mass was noted at the anteromedial aspect of the right knee without a needle track or skin lesion indicating trauma.

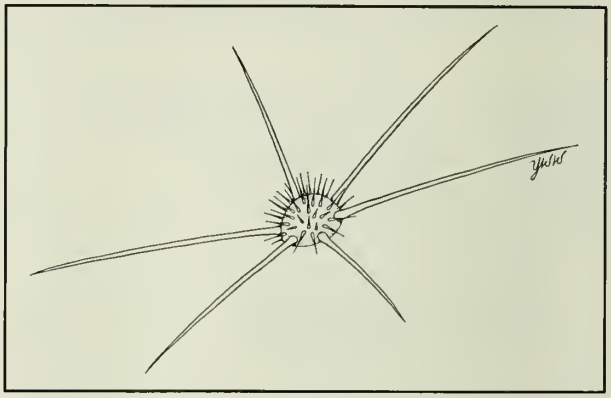

Figure 3.—An *Echinocerus pectinatus* shows distinctly different thorn types. The small thorns are difficult to remove because of the large number that usually superficially embed in the skin. A large thorn can deeply embed, such as in this case, without leaving a visible skin mark.

cactus species have two varieties of thorns (Figure 3), including the species in this case, *Echinocerus pectinatus*. In this patient, the small (1 mm in length) thorns removed from the skin were distinctly smaller than the surgically removed 40-mm thorn from the same plant, a fact that clouded the diagnosis. The MRI of the thorn showed a thin dark line that does not approximate any normal pathologic disorder and was initially interpreted as artifact, so the importance of this case extends as well to radiologists and other physicians interpreting magnetic resonance images.

The literature identifies a variety of types of microbiologic and antigen-induced inflammation as sequelae of embedded cactus thorns.[2-7] Although fungal contamination of thorns can cause infections, this is unusual, as is consistent with this case. This case was typical in that an active inflammatory response to the thorn was present, but no bacteria were identified. Synovitis has been reported as a response to a cactus thorn in the knee joint,[8] as well as tendinitis and myositis from soft tissue penetration.[9,10] Most reports of cactus thorns describe thorns embedded in the foot, knee joint, or upper extremity. The unusual location of this thorn in the patient's cartilaginous epiphysis serves to illustrate the sharpness and strength of the cactus thorn, characteristics often underestimated. This location is also relevant as a possible cause of growth abnormality or chronic infection.

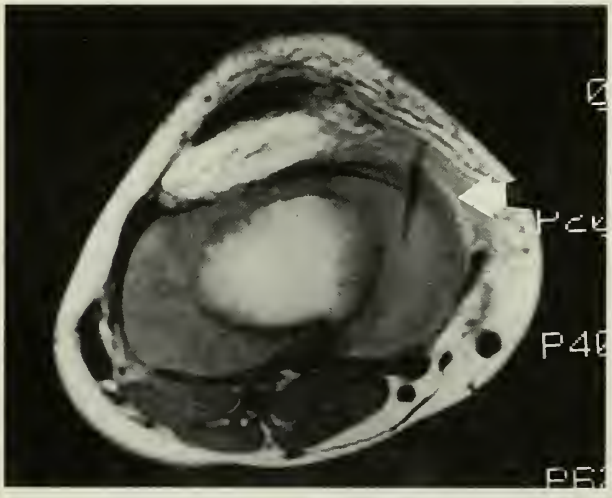

Figure 2.—The patient's T2-weighted transverse plane magnetic resonance image shows a conical foreign body signal in the cartilaginous tibial epiphysis that was initially interpreted as artifact.

Reports of operative treatment of embedded thorns have prominently mentioned difficulties in finding and removing the thorns from soft tissue and joints.[1,11,12] Cactus thorns are radiolucent and cannot be localized or distinguished from surrounding soft tissue by plain radiography. A thorn in the knee joint is difficult to find on surgical exploration. The MRI was helpful in making the diagnosis and localizing the thorn. These results support the use of MRI when cactus thorn foreign bodies are considered in the differential diagnosis, especially when surgical removal is planned.

The observed worsening condition, operative finding of localization, and good short- and long-term results demonstrated in this patient all show the appropriateness of operative treatment. The risk of cartilaginous infection or cartilaginous growth abnormality cannot be determined from this report, but the outcome supports the use of debridement, as performed in this case. Although most common in the southwestern United States, cactus thorn injuries can occur anywhere due to the prevalence of ornamental cacti in households across the country, making cactus thorn foreign body penetration a candidate for differential diagnosis regardless of locale.

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Mixed Bacterial Meningitis in a 4-Year-Old Girl

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REPORTS OF MIXED BACTERIAL MENINGITIS date back to the early 1930s. Recent data suggest that this disorder constitutes about 1% of the total cases of meningitis.[1] Epidemiologic studies show a change in disease pattern from a community-acquired childhood infection to a mainly nosocomially acquired adult illness, particularly in those with defects near the meninges. We report an unusual case of a healthy child with mixed bacterial meningitis due to a *Streptococcus pneumoniae* species and a nontypable strain of *Haemophilus influenzae*.

Report of a Case

The patient, a 4-year-old girl who was in good health since birth and had an up-to-date immunization history, was seen by her physician after one day of fever, headache, vomiting, and a rapid deterioration in her mental state. She had pronounced nuchal rigidity suggesting meningitis. A lumbar puncture revealed turbid cerebrospinal fluid (CSF) with 440×10^6 leukocytes per liter (0.80 neutrophils, 0.10 lymphocytes, and 0.10 monocytes), a glucose level of less than 1.1 mmol per liter (20 mg per dl) with a serum glucose value of 24.4 mmol per liter (144 mg per dl), and a protein level of 1.46 grams per liter (146 mg per dl). A CSF Gram's stain showed 4+ gram-positive cocci. The patient was transferred to hospital for further management.

(Chokephaibulkit K, Leo YS, Wittek AE: Mixed bacterial meningitis in a 4-year-old girl. West J Med 1995; 162:59-60)

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On admission the patient was lethargic and disoriented and had intermittent opisthotonic posturing. A regimen of intravenous cefotaxime sodium, 200 mg per kg of body weight per day, and dexamethasone, 0.6 mg per kg per day, was started within 15 minutes, and she was placed in the intensive care unit. Shortly after admission, she became flaccid and showed only minimal response to painful stimuli. Her pupils were equal, but reacted sluggishly to light. Mild papilledema was noted. A brain computed tomographic (CT) scan confirmed the presence of diffuse cerebral edema with compression of the ventricles and cisterns. In addition, findings consistent with pansinusitis were noted. An endotracheal tube was electively inserted for hyperventilation therapy.

Further laboratory tests revealed that the patient had disseminated intravascular coagulation as evidenced by a prothrombin time of 17.2 seconds, a partial thromboplastin time of 47.2 seconds, D-dimer greater than 8,000 ng per ml, and a platelet count of 205×10^9 per liter (205×10^3 per mm^3). Her serum sodium level was 126 mmol per liter, potassium 3.5 mmol per liter, and serum osmolarity 270 mmol per kg (270 mOsm per kg), suggestive of the syndrome of inappropriate antidiuretic hormone (ADH) secretion. *Streptococcus pneumoniae* was identified in cultures of blood and CSF specimens obtained on admission. The following day, a nontypable *H influenzae* strain was identified in the same culture of CSF. The patient regained consciousness the next day and showed no further laboratory evidence of disseminated intravascular coagulation or the syndrome of inappropriate ADH secretion.

On the third hospital day, the patient was extubated and remained stable. A follow-up CT scan of the brain showed marked lessening of the cerebral edema. On the fifth day the patient became afebrile. She received intravenous cefotaxime for a total of 14 days, followed by the combination of amoxicillin and clavulanic acid for another seven days because of the CT evidence of sinusitis. The patient continued to show progressive improvement and on day 18 was transferred to a rehabilitation facility with only mild peripheral weakness and a mild residual dysarthria. Her brain-stem auditory evoked potentials and vestibular evoked potentials were within normal limits on discharge. Her residual neurologic abnormalities resolved slowly over several weeks.

Discussion

The incidence of mixed bacterial meningitis is highly variable, ranging from near 0% to 14%.[2-4] The disease pattern has changed over the past two to three decades from a primarily community-acquired childhood disease to a disease mainly seen in adults, with a high incidence of nosocomial acquisition.[1] Today, mixed bacterial meningitis accounts for about 1% of the total cases of meningitis. Of these, about 90% of the patients suffer from a predisposing condition that can be identified, including recent neurosurgical procedures, indwelling intracranial catheters, malignancy adjacent to the central nervous system axis, disruption of an anatomic barrier such as a neurocutaneous fistula, and posttraumatic CSF leak.[1,5-8]

ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
CSF = cerebrospinal fluid
CT = computed tomographic

In an extensive review of the English-language literature, the changing patterns of offending pathogens in mixed bacterial meningitis beyond the newborn period were clearly documented.[1] Before 1950, *H influenzae* was the most common bacterial organism identified, followed by *S pneumoniae* and *Neisseria meningitidis*. Occasionally *Escherichia coli* and *Klebsiella* species had been isolated. As expected, these are the common childhood meningeal pathogens. Among cases of mixed bacterial meningitis diagnosed after 1950, the vast majority were due to more virulent gram-negative rods such as *Pseudomonas*, *Klebsiella*, and *Enterobacter* species and occasionally *Staphylococcus aureus* and anaerobic bacteria. Most of these pathogens were nosocomially acquired. Our patient's illness resembled those cases of mixed bacterial meningitis diagnosed in the early years with the involvement of *S pneumoniae* and *H influenzae*.

Of interest in this case is the isolation of a nontypable strain of *H influenzae*, which is an uncommon pathogen in meningitis, especially beyond the newborn period.[9] The incidence of invasive disease caused by nontypable *H influenzae* in children younger than 10 years is on the order of 0.5 per 100,000, which accounts for about 6% of all cases of invasive *H influenzae* infections. Many patients with invasive nontypable *H influenzae* infection have serious underlying illness such as acute lymphoblastic leukemia and spina bifida and also tend to have a primary focus of infection adjacent to the respiratory tract. These findings all together support a less virulent nature of this organism.[9] The use of the Hib vaccine resulted in eradicating *H influenzae* type B from the nasopharynx[10] and may increase the proportion of nontypable *H influenzae* colonization with a concomitant higher infection rate. This may have been the case in our patient, who received her Hib vaccination at 18 months.

The pathophysiology of mixed bacterial meningitis in cases without a predisposing condition remains unclear. Studies of animals demonstrate that meningitis often results from invasion of bacteria resident in the upper respiratory tract into the blood stream with subsequent seeding of the meninges.[11] A preceding upper respiratory tract infection that alters or compromises local immunity may facilitate the invasion of more than one organism at a time. This hypothesis explains the observation that *H influenzae*, *S pneumoniae*, and *N meningitidis* are the most common pathogens in childhood meningitis, mixed or otherwise, because they are among the most common pathogens colonizing the upper respiratory tract in children.

From earlier reports, sinusitis and otitis media are relatively common predisposing factors for childhood mixed bacterial meningitis, although brain abscess has been a more commonly reported complication of both these conditions. Mixed bacteria, including anaerobes, are not infrequently isolated in these two conditions.[8,12-14] Thus, in our patient, mixed bacterial meningitis may have been a result of an incidental simultaneous invasion of two organisms from the upper respiratory tract or, given the presence of a parameningeal focus on CT scan, the result of direct invasion of the organisms from her infected sinuses.

Clinically, this disorder seems to be more aggressive than meningitis due to a single pathogen, with a higher mortality rate.[1,3] The differences are probably the result of the underlying disease and the presence of more virulent bacteria, such as the nosocomial gram-negative bacilli involved in many cases. In this patient, the clinical presentation was indistinguishable from that caused by a common single pathogen. Microbiologic identification in her case was crucial to making the diagnosis. In cases of community-acquired meningitis, even in the mixed bacterial type, most pathogens are sensitive to the antibiotics routinely used in recommended empiric therapy. In cases of meningitis with evidence of concomitant sinusitis or otitis media, however, caution should be exercised in tailoring antibiotic therapy to the causative organism. In the era of penicillin-resistant *Pneumococcus* species, the empiric antibiotic should not be changed until final culture results and sensitivities are known. Finally, in all patients with spontaneous mixed bacterial meningitis, underlying predisposing conditions such as sinusitis, otitis, and neurocutaneous or neurenteric fistulae should be actively looked for, particularly in the presence of other congenital anatomical defects.

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Reactive Arthritis Following *Clostridium difficile* Colitis

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REACTIVE ARTHRITIS is a recognized sequela of infection with a number of enteric pathogens. *Yersinia enterocolitica*,[1] *Campylobacter jejuni*,[2] and *Salmonella typhimurium*[3] enteritis can all cause reactive arthritis. A 1962 shipboard outbreak of *Shigella* species dysentery from contaminated food offered further insight into the natural history and epidemiologic features of Reiter's syndrome, a variant of reactive arthritis. Nine cases of Reiter's syndrome followed directly from 602 cases of shigellosis.[4] Reports have recently appeared of reactive arthritis occurring after *Clostridium difficile* infection, usually in patients with colitis associated with antibiotic therapy.[5] We describe the case of a patient who clearly had reactive arthritis from *C difficile* colitis and add this case to the growing number of articles on this infrequently recognized but important association between two common diseases.

Report of a Case

The patient, a 26-year-old United States Navy sailor, had the sudden onset of right second metatarsophalangeal arthritis with associated overlying erythema a week after completing a month-long course of serial antibiotics—erythromycin, the combination of amoxicillin and clavulanate potassium, and the combination of trimethoprim and sulfamethoxazole—for presumed sinusitis. His primary care physician diagnosed cellulitis in him and prescribed a course of dicloxacillin sodium. Over the ensuing two weeks, an additive oligoarthritis involving the left ankle, the right wrist, and the right subacromial region developed. The erythema and tenderness about the metatarsophalangeal joint did not resolve with the course of antibiotics, and the patient was referred to our institution for evaluation. He reported having no previous episodes of a similar illness, rash, sexually transmitted disease exposure, photophobia, or urethritis. He was sexually monogamous with his wife of five years.

At admission, the patient was well developed and well nourished and had a temperature of 38.2°C (100.8°F), pronounced tenderness of the right second metatarsophalangeal joint, and extensive erythema and swelling across the dorsum of the right foot without lymphangitic streaking or adenopathy. He had synovitis of the left ankle, the right wrist, and the right subacromial area. He notably showed no evidence of conjunctivitis, oral ulcers, rash, meatal inflammation, urethritis, or penile discharge.

Laboratory tests revealed a mild leukocytosis (13.2×10^9 per liter [13.2×10^3 per mm^3] with a normal differential), an erythrocyte sedimentation rate of 51 mm per hour, and a normal serum uric acid level. Urethral Gram's stain and culture for both gonococci and chlamydia were negative. Blood cultures were negative for pathogens. Aspiration of the left ankle removed 7 ml of cloudy, turbid, nonpurulent, inflammatory synovial fluid with a leukocyte count of 17.32×10^9 per liter (17,325 per mm^3). No crystals were seen with polarizing microscopy. Coccidioidomycosis, rheumatoid factor, Lyme, antinuclear antibody, and antistreptolysin-O titers were negative. Subsequently, all synovial fluid cultures (including acid-fast bacilli and fungi) were negative.

Three days after admission the patient had loose, watery, nonbloody diarrhea. On further questioning he recalled a similar episode of six to eight loose bowel movements per day for about three days, preceding the arthritis by a week. A stool culture for common enteric pathogens—*Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* species—was negative. Sigmoidoscopy revealed nonspecific segmental colitis. Stool *C difficile* "A" toxin was identified by rapid enzyme-linked immunosorbent assay (ELISA). The patient was diagnosed with antibiotic-associated colitis and treated with metronidazole. The diarrhea promptly resolved, and there has subsequently been no recurrence of bowel symptoms.

The arthritis persisted despite toxin assays that were subsequently negative for *C difficile*, and the patient required the intraarticular administration of corticosteroids several times. The HLA-B27 antigen was found to be present. Six weeks later, as the arthritis was slowly resolving on a regimen of indomethacin (50 mg by mouth 3 times a day), the patient presented with noninfectious urethritis and several oral ulcers. Cultures of specimens from both the patient and his wife were again negative for *Chlamydia* species and *Neisseria gonorrhoeae*. A trial of therapy for reactive arthritis was begun with sulfasalazine, initially given as 500 mg a day and raised to 1.0 gram a day. This was stopped after three weeks when a truncal rash and transient aminotransferase elevations developed. Over the ensuing six months, there was some gradual joint improvement on the indomethacin regimen alone, although he had persistence of synovitis in both ankles and the right wrist.

Discussion

Antibiotic-associated colitis results when antibiotic-induced disturbances of the gut flora allow for bacterial overgrowth, usually with toxigenic *Clostridium difficile*.[6] The resultant diarrhea may occur concomitant with antibiotic administration or within four weeks of its discontinuation. Almost every antibiotic has been implicated, although the most common are clindamycin, ampicillin,

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and the cephalosporins. This disorder occurs along a spectrum from mild, annoying diarrhea to fulminant, life-threatening toxic megacolon.[7] Diagnosis is usually made by ELISA testing for *C difficile* toxin in the stool. Although asymptomatic carriage may occur, especially in patients in hospital, a positive toxin titer in a patient with colitis with previous antibiotic exposure is regarded as highly specific for *C difficile* colitis. Metronidazole or vancomycin hydrochloride by mouth are usually effective in eradicating the diarrhea, although relapses occur in about 25% of patients.[8]

Reactive arthritis is defined as the occurrence of an acute, aseptic, inflammatory arthropathy arising after an infectious process, but at a site remote from the primary infection.[1] The arthritis typically involves the large and medium joints of the lower extremities and first manifests one to four weeks after the infectious insult. Associated findings may include uveitis, enthesitis, mucocutaneous lesions (circinate balanitis, keratoderma blennorrhagicum), sacroiliitis, dactylitis, urethritis, and conjunctivitis.[9] A subgroup of patients with reactive arthritis demonstrates the classic clinical triad of arthritis, urethritis, and conjunctivitis, which is called Reiter's syndrome.[10] Reactive arthritis may include some, but not all, of the three features associated with Reiter's syndrome. The distinction between Reiter's and reactive arthritis is somewhat arbitrary, and in clinical practice, reactive arthritis is often designated "incomplete Reiter's syndrome."

A particular major histocompatibility complex class I antigen, HLA-B27, is well-recognized as a genetic marker of susceptibility to reactive arthritis. Most patients susceptible to this form of arthritis possess the HLA-B27 antigen. In classic Reiter's syndrome, 60% to 80% of patients will prove positive when tested for this antigen. This frequency is dependent on the gene frequency in the study population, so that 75% to 80% of white Americans and fewer than 50% of African Americans with classic Reiter's syndrome will have the HLA-B27 antigen.[11]

The relationship of the "gut" to the "joint" is an intriguing one. Intestinal bypass syndrome, inflammatory bowel disease, Whipple's disease, ankylosing spondylitis, collagenous colitis, celiac disease, parasitic rheumatism, postdysenteric reactive arthritis, and antibiotic-associated colitis all share the fact that some "interface" between the bowel and the articular surface is involved in disease pathogenesis.[12,13]

The clinical expression of joint disease has been hypothesized to result from an immunologic response to an antigen that crosses the gut mucosa, with the perpetuation of an immune response against the "self." Perhaps colonic inflammation, from whatever cause, allows for some gut antigen to cross the mucosal barrier, resulting in synovitis and immune-mediated joint disease.[12] Curiously, Hans Reiter initially described the triad of nongonococcal urethritis, conjunctivitis, and polyarthritis in a young World War I soldier after an episode of bloody diarrhea.[14]

A case of antibiotic-associated colitis causing reactive arthritis was first described in 1976, before the understanding that *C difficile* was the likely causative agent of the colitis.[15] The connection between antibiotic-associated (or *Clostridium difficile*) colitis and reactive arthritis has become clearer as our understanding of these two diseases has expanded. A total of 17 cases have now been reported, although 2 were from the period before an attempt could be made to identify *C difficile*. All were recently reviewed.[5] Clindamycin was most frequently the inciting antibiotic for the antibiotic-associated colitis. Various joints become involved, with the occurrence of arthritis usually following the episode of diarrhea by 8 to 35 days, with a mean of 18 days. No particular characteristics seemed to differentiate the reactive arthritis of *C difficile* from other forms of reactive arthritis. HLA-B27 testing was done in 14 patients and was positive in 8 (57%). The antigen was more frequently seen in men (4/5, or 80%) than in women (4/9, or 44%). In the 6 cases with available follow-up, the overall prognosis appeared good, as 5 were asymptomatic at a follow-up period of 1 to 20 months. The sixth patient still suffered from mild sacroiliitis and knee arthralgias at two years and was treated intermittently with nonsteroidal anti-inflammatory drugs. The arthritis, in general, persisted longer in those who were HLA-B27–positive.

Our patient was notable from the standpoint of his persisting symptoms at six months, similar to the sixth patient described above. This was at odds with the excellent prognosis observed in the other cases of *C difficile*-associated reactive arthritis in which follow-up was reported. The overall prognosis for reactive arthritis is good, but we know from earlier studies with Reiter's syndrome that full recovery does not always occur, and many patients will face some form of persisting symptoms that can lead to chronic disability.[16] Certainly, prompt treatment of the colitis cannot be relied on to avert the development of a reactive arthritis. The presence of the HLA-B27 antigen might be interpreted as portending a prolonged bout of synovitis, but further work in this area is necessary.

This case of reactive arthritis subsequent to *C difficile* colitis represents an unusual manifestation of a common complication of antibiotic therapy. Physicians caring for a patient with an acute inflammatory arthritis of one or several joints should query that patient carefully about recent antibiotic exposure and consider stool testing for *Clostridium difficile* in those with diarrhea.

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Vasculitis Possibly Confined to the Small and Large Intestine

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VASCULITIS OF THE GASTROINTESTINAL TRACT is an uncommon disorder and typically accompanies systemic manifestations of a vasculitic process.[1] We report a case of isolated gastrointestinal vasculitis affecting both the small and large intestine.

Report of a Case

The patient, a 73-year-old woman with a history of controlled hypertension, deep venous thrombosis of the calf in 1982, and a minor cerebrovascular accident in 1976, presented to her primary physician six months before admission with progressive, diffuse, crampy abdominal pain exacerbated by eating and associated with weight loss. Three months before admission she had bloody diarrhea, and a flexible sigmoidoscopy revealed diffuse redness and friability in the rectosigmoid area. Biopsies revealed nonspecific acute and chronic mucosal inflammation. A computed tomographic scan of the abdomen, air-contrast barium enema, and an esophagogastroduodenoscopy were normal. Abdominal ultrasonography was unremarkable, other than for the presence of gallstones. Laboratory data included a hemoglobin level of 80 grams per liter (8 grams per dl), with a mean cellular volume of 73 fl, and liver function test values were normal. The patient was treated with metronidazole for presumed infectious colitis, without benefit. She also received ferrous sulfate, and her hemoglobin value increased to 137 grams per liter (13.7 grams per dl) over the next six weeks. A month before admission, the patient continued to have abdominal pain and hematochezia, and her hemoglobin level had dropped to 85 grams per liter (8.5 grams per dl).

The patient was admitted to a community hospital where a flexible sigmoidoscopy revealed rectosigmoid friability without ulceration. A presumptive diagnosis of ulcerative colitis was made. Treatment with sulfasalazine (Azulfidine) and methylprednisolone sodium succinate (Solu-Medrol), 40 mg a day intravenously, was begun. Two days later an acute abdomen developed, and the patient's leukocyte count was noted to be 40×10^9 per liter (40,000 cells per mm^3). The patient was taken to the operating room where extensive small bowel necrosis with gangrene was found. The small bowel was resected from the midjejunum to the ileocecal valve, and a right hemicolectomy was performed because the colonic serosa appeared dusky. Mesenteric arterial pulsations were thought to be within normal limits, mesenteric veins did not appear unusual, and a jejunocolostomy was done. Microscopic review of the specimens showed transmural necrosis of the bowel, consistent with ischemic necrosis, and the presence of thrombi in small mesenteric veins.

After the operation, the patient had diarrhea and recurrent hematochezia. Esophagogastroduodenoscopy was within normal limits, and a flexible sigmoidoscopy revealed mild erythema and edema to 50 cm without ulceration or friability. This was thought to be an improvement from the previous examination, and her steroid regimen was tapered off. Persistent hematochezia requiring the transfusion of 10 units of packed erythrocytes prompted a mesenteric angiogram, which revealed grossly normal superior and inferior mesenteric arteries without aneurysms or atherosclerotic disease. A blush without extravasation was seen in the midjejunum, consistent with an arteriovenous malformation.

Two weeks later the patient was transferred to the University of California Center for Health Sciences at Los Angeles (UCLA) for further management. At that time she had mild abdominal pain. The patient had no visible skin or joint lesions, and her stools were brown and positive for occult blood. Push enteroscopy with a Pentax 3400 colonoscope revealed three nonbleeding arteriovenous malformations in the antrum, proximal duodenum, and proximal jejunum, respectively, which were treated with bipolar electrocauterization. Colonoscopy to the surgical anastomosis revealed swollen mucosal folds with a loss of the normal vascular pattern throughout. There were ulcerations in the rectum and severe nodularity with punched-out ulcerations in the mid-sigmoid colon (Figure 1). The anastomotic site was deformed and friable and could not be traversed. Endoscopic biopsies from the involved colon again revealed acute and chronic mucosal inflammation without specific features.

Histology slides and gross specimens from the previous small and large bowel resection were then re-

(Freilich BL, Bernstein CN: Vasculitis possibly confined to the small and large intestine. West J Med 1995; 162:63-65)

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Dr Bernstein's work is supported in part by the Blinder Foundation for Crohn's Disease Research.

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Figure 1.—Endoscopy of the sigmoid colon reveals multiple punched-out ulcers and underlying nodular edematous mucosa.

viewed at UCLA. The small intestine showed transmural ischemic infarction with ulceration and acute inflammation throughout the bowel wall (Figure 2). In addition, sections of the mesentery revealed acute vasculitis of many medium-sized arteries in areas remote from the bowel necrosis and inflammation. The vasculitis was characterized by a neutrophilic infiltrate of the vessel walls and disruption of the internal elastic lamina with fibrinoid necrosis and thrombosis (Figure 3). No giant cells or granulomas were seen.

Echocardiogram showed no evidence of thrombus and a normal myocardium. Her urinary sediment was bland without casts or erythrocytes, and a 24-hour urine collection revealed a creatinine clearance of 1.12 ml per second

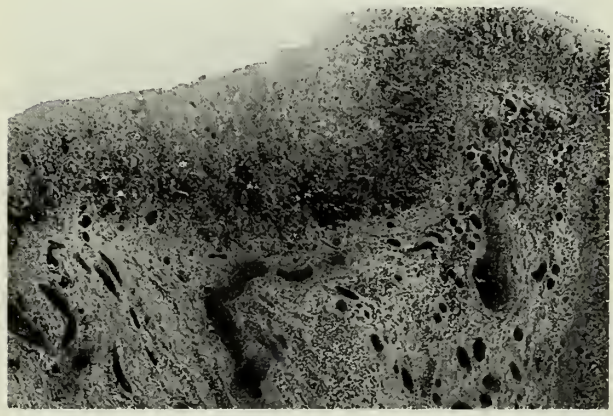

Figure 2.—A low-power view of the small bowel wall shows necrosis of the mucosa and submucosa. Many small submucosal vessels are dilated and congested, and an acute and chronic inflammatory infiltrate is present throughout the bowel wall (hematoxylin and eosin stain, original magnification × 25).

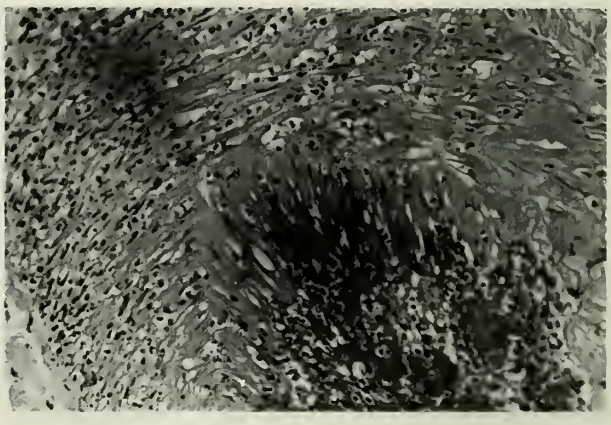

Figure 3.—A high-power view of the small bowel wall shows a medium-sized artery in the small bowel mesentery. All levels of the artery wall are infiltrated by acute inflammatory cells. The intima shows fibrinoid necrosis, and the vessel is thrombosed (hematoxylin and eosin stain, original magnification × 200).

(67 ml per minute) and a protein concentration of 0.14 grams per day (135 mg per 24 hours). Serologic examination revealed normal blood urea nitrogen and serum creatinine levels; negative titers for rheumatoid factor, antinuclear antigen, and antineutrophilic cytoplasmic antibody; a negative Raji assay; and normal complement levels. Antithrombin III and protein C and S levels were normal. A high titer of the lupus anticoagulant was found, although assay for anticardiolipin antibody was negative.

The patient was diagnosed with vasculitis of the small intestine and colon, and intravenous therapy with methylprednisolone, 50 mg per day, was begun. Her previous gastrointestinal bleeding was ascribed to diffuse colonic oozing due to severe ischemic colitis and did not recur while she was at UCLA. She was maintained on total parenteral nutrition and enteric supplements. Her diarrhea persisted and was thought to be predominantly due to a short gut syndrome.

Discussion

This case is one of isolated small and large intestine vasculitis. It is unique because it is the first case of isolated intestinal vasculitis reported to involve both the small and large intestine and is only the fifth case in the literature of isolated intestinal vasculitis without systemic signs of vasculitis.[2-5] This patient more likely had systemic vasculitis (with a positive lupus anticoagulant) with isolated intestinal manifestations, rather than primary intestinal vasculitis. Other cases of isolated intestinal vasculitis have had pathologic findings consistent with more diffuse processes. A case of isolated small intestinal vasculitis leading to perforation and death was reported, with autopsy findings consistent with polyarteritis nodosa.[2] In another case, isolated giant cell arteritis occurred, leading to intestinal perforation,[3] and a case of isolated ileal vasculitis as a paraneoplastic syndrome to a recurrent breast adenocarcinoma was also reported.[4] The disease in these three cases was limited to the small intestine. A case of isolated vasculitis was limited to the right colon, with pathologic

findings consistent with granulomatous inflammation and necrotizing vasculitis, possibly polyarteritis nodosa, selectively involving branches of the right colic artery.[5]

Gastrointestinal vasculitis is a fairly uncommon disorder and often difficult to diagnose. Patients frequently present with bloody diarrhea and abdominal pain, and the disease may ultimately lead to intestinal ischemia and perforation.[1] Ischemia from vasculitis is clinically similar to atherosclerotic and embolic disease[6] and can be confused with Crohn's disease.[5]

One group of investigators has suggested that careful histologic examination of the intestinal mucosa in Crohn's disease may reveal a granulomatous vasculitis,[7] and there are reports of cutaneous vasculitis[8,9] and the presence of anticardiolipin antibodies[10,11] in patients with Crohn's disease. Our patient did not have granulomatous vasculitis, and vasculitic arteries were often present in areas remote from areas of inflammation (which is unusual in Crohn's disease). Furthermore, extensive intestinal infarction is not a feature of Crohn's disease. Another of the idiopathic forms of inflammatory bowel disease, ulcerative colitis, is a disorder confined to the mucosa of the large intestine. There are reports of occasional instances of systemic vasculitis in association with ulcerative colitis,[9] including cutaneous polyarteritis nodosa,[12] systemic lupus erythematosus,[13] and Wegener's granulomatosis.[14] Ulcerative colitis can be associated with the presence of an antineutrophilic cytoplasmic antibody (that stains in a perinuclear pattern on immunofluorescence, as opposed to the more typical cytoplasmic granular pattern in Wegener's granulomatosis) in 70% of patients.[15] Our patient's disease was certainly not ulcerative colitis, as it extended to the small intestine and was associated with transmural inflammation.

Gastrointestinal vasculitis is almost always accompanied by systemic manifestations of disease. The largest series of such patients was reported in 1983, wherein 18 of 65 patients with systemic vasculitis had disease affecting the gastrointestinal tract.[1] Most of these patients had polyarteritis nodosa or microscopic polyarteritis (disease affecting small vessels with normal angiograms). Wegener's granulomatosis and the Churg-Strauss syndrome were found less commonly. Of the 18 patients with gastrointestinal manifestations, 17 had focal glomerulonephritis on renal biopsy, and all had clinical signs of glomerulonephritis. Necrotizing vasculitis was found on skin biopsy in 6 of 18 patients with purpuric lesions. Other connective tissue diseases more commonly associated with gastrointestinal vasculitis include systemic lupus erythematosus,[17] rheumatoid arthritis, and hypersensitivity vasculitides.[18]

Angiographic findings are generally remarkable only in cases of polyarteritis nodosa where aneurysms are found in medium-sized mesenteric vessels.[1] Endoscopic diagnosis is also challenging, as routine luminal biopsy specimens through flexible endoscopes rarely show the diagnostic lesions. Deep rectal biopsies through rigid proctoscopes, however, may have a slightly higher yield.[16] Often the diagnosis is a clinical one, with intestinal disease accompanying other systemic signs of vasculitis.

Our case was also complicated by the presence of mesenteric vein thromboses. These thrombi were likely due to intestinal vasculitis and gangrene, as they were not organized thrombi and, therefore, not chronic. Primary thrombus due to the lupus anticoagulant cannot be ruled out, however, especially in light of the patient's history of previous thrombotic events. The presence of the lupus anticoagulant may indicate that the patient had a truly systemic vasculitis, but presented without nongastrointestinal manifestations. There have also been reports of necrotizing vasculitis involving the mesenteric veins of patients with primary mesenteric vein thrombosis.[19] None of these patients had evidence of arterial vasculitis, as did our patient.

Intestinal ischemia with perforation or gangrene is an abdominal catastrophe with many causes. Vasculitis can certainly be one such cause, albeit rare. Our case reinforces that gastrointestinal vasculitis may present without systemic manifestations of vasculitic disease and may affect both the colon and small intestine.

Acknowledgment

Marie Robert, MD, Department of Pathology, UCLA, assisted with the histopathology in this case.

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Commentary

Al-Kindi—Physician, Philosopher, and Savant Seven Centuries Before the Renaissance

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Physicians have made important contributions not only to medicine but to other areas of human endeavor and culture. Perhaps no physician provides a more dramatic example of this than the Arab physician, Abu Yusuf Ya' qub lbn Ishaq al Kindi, usually identified as al-Kindi. Despite his unusual contributions to many fields of human endeavor, he remains virtually unknown to western medicine.

The exact dates of al-Kindi's birth and death are not recorded, but he lived in the ninth century AD (western calendar), third century AH (after the Hegira-Islamic calendar). He was born of noble descent in Basra, a southern Iraqi city on the Persian Gulf. Most of his adult life was spent in Baghdad. A number of his writings have been lost over the last millennium, but the remaining works show an amazing range of interests and a high degree of productivity.

Our essay was compiled from secondary sources because the original sources are difficult to locate—neither of us is familiar with the Arabic language, and translations are rare. For example, al-Kindi's studies on drugs and drug interactions and his treatment of cost-benefit analysis are completely modern.

In addition to general philosophy and medicine, al-Kindi contributed to our knowledge of metaphysics, psychology and its application to psychotherapy, astronomy, astrology, cosmology, optics, perfume distillation, music and its use as a psychotherapeutic tool, implements, including the manufacture of swords, scientific instruments, musical instruments, especially the lute, pharmacology, geography, chemistry, gemology, literature, zoology, sociology, and mathematics.

Given the scope of al-Kindi's surviving writings, it is tempting to consider him a dilettante, flitting from interest to interest at a superficial level. But he was not. He pursued his many disciplines with a depth and a degree of specificity that indicated both profound involvement and studious attention to detail.

For example, his writings on optics are still regarded as important and surprisingly modern contributions to the theories of vision. It has been speculated that his interest in eyesight stemmed from the high prevalence of eye disease in that area of the world—trachoma, for example, is still a common cause of blindness in much of the Middle East.

The list of al-Kindi's areas of proficiency establishes another aspect of his work—the application of technology to medicine. The process of perfume distillation and manufacture is not very different from the preparation of medicinals. An expert in the manufacture of swords might use this knowledge in fabricating surgical instruments.

We know al-Kindi applied many of these technologic methods to medicine. He was an early contributor to the flood of technical applications that now so deeply affect medical practice.

His contributions to music included not only general material, but also a volume on string instruments and treatises on the composition of a melody and the manufacture of a lute. He was an ardent experimentalist centuries before formal experiments were known in the western world, as illustrated by these quotations: "This could be easily explained by observing an experiment to illustrate it. Take a bottle . . . " and "We tried because carrying out an experiment was quite possible, and we believe that when a statement is based on an experiment that can be sensed, that it cannot be discredited except by proof that it does not happen. Therefore, we have made our own projectile to carry on an experiment."

He was an early advocate of applying international standards to the search for truth: "We should not be ashamed to acknowledge truth from whatever source it comes to us, even if it is brought to us by former generations and foreign peoples. For him who seeks the truth . . . there is nothing of higher value than the truth itself."

We are, of course, primarily interested in his contributions as a physician. His writings embraced virtually all branches of human knowledge in medieval times, and he was able to apply his encyclopedic knowledge to medicine.

This list of his published works on medicine illustrates the range of his medical interests.

On Hippocratic Medicine (al-Kindi was an avid student of Greek philosophy and medicine)

On Virulent Drugs

On Vapors Which Ameliorate the Atmosphere From Plague

On Drugs Which Heal From Harmful Odors

(Robin ED, Notkin H: Al-Kindi—Physician, philosopher, and savant seven centuries before the Renaissance. West J Med 1995; 162:66-67)

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†Dr Notkin died November 18, 1994. This communication is a memorial to him.

On Illness Which Produces Blood Spitting
On Antidotes
On Preservation of Health (Was he a forerunner of advocates of preventive medicine?)
On the Delirium of Acute Disease
On the Soul of the Body's Major Organ (the brain)
On the Brain
On Leprosy and Its Treatment
On Mad Dog Bites
On Symptoms Resulting From Phlegm and the Cause of Sudden Death
On Stomachache and Gout
On Kinds of Fever
On Medical Treatment of Morbid Hardening of the Spleen
On Decomposed Animal Bodies
On Recognizing the Great Value of the Healing Art
On Food Made of Substitute Ingredients
On Adulteration of Food
An Introduction to the Healing Arts

One of al-Kindi's most valuable contributions to medicine was his formulary, which is notable not only for its broad range of drugs, but also because he explicitly recognized his limitations of knowledge. Almost all his formulations end with statements like "It (the mixture) is efficacious if God wishes." Such comments must be tempered by the fact that al-Kindi was a devout Moslem. Moslems believe that God (Allah) decides all things. *Insh' Allah* ("God willing") is customarily invoked at the end of the most simplistic discussion of the future. For example: "I will meet you tomorrow, *Insh' Allah*."

In a modern fashion, al-Kindi explicitly recognized the importance of drug interactions, but chiefly from the standpoint of benefits rather than risks: "Greek physicians discussed the faculties and qualities of simple drugs only. But they failed to do so in regard to compound medications which appear even more significant."

Given the broad range of his interests in medicine, it is not surprising that he anticipated cost-benefit analysis:

> If, in seeking to be healed from diseases of the body, we bear the bitterness of medications, the suffering of cauterization and surgery [al-Kindi was no surgeon] and be willing to spend large sums of money for medical care. . . [An early attempt at health care reform?]

We know little of his specific activities as a clinician, although he was directly involved in patient care. One of his surviving works is a letter to a patient. He presumably used the medical school in Baghdad as an operational base. Eleven centuries before the Flexner Report, Arab medical schools apparently used the bedside manner of teaching. We can assume that al-Kindi was a master bedside teacher.

It is interesting to note that today's formal western medical literature contains only two paragraphs summarizing his medical contributions (M. A. Shampo, R. A. Kyle, "Yusuf Ibn Al-Kindi," *Journal of the American Medical Association* 1975; 234:165). Few standard medical history books even mention him, although his work appears to have influenced the development of modern medicine. Al-Kindi's works provide a number of lessons. Genius knows no geographic, ethnic, or political boundaries. It flows from some genetic and environmental mixture that may be found anywhere at any time. The form of genius that makes important contributions in many unrelated human intellectual activities is exceedingly rare. Al-Kindi was a spectacular and unique example. One characteristic of such persons is that they apply approaches that may have long-term time effects. This philosopher-savant provided approaches that are still useful 11 centuries after his death. His wide use of technology and its application to medicine anticipated the flood of technology that dominates medicine today. It is, therefore, appropriate to pay tribute to a Renaissance man who lived some 500 years before the European Renaissance.

I have provided a brief bibliography on al-Kindi. Interested readers may write to me for a more complete summary of references.

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Commentary

Can the Specialist Be a Generalist?

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There currently is a perceived or real shortage of practicing generalist physicians in the United States. One suggested remedy is to retrain specialists to gain primary care competence.[1-5] This solution begs a very big question: Can a specialist be a generalist? If the question is posed in this manner, the answer must be "Yes, but not easily." Can a professional football player be a ballet star? Can a rabbi be a priest? Yes, but not easily and perhaps not advisably. A more germane question is "Will a specialist choose to be a generalist?" or "Should a specialist be a generalist?"

In part, the answer depends on some specifics. Are we proposing a national mandate or policy, or are we asking if this can be done in certain circumstances? Also, all specialists are not the same. Are we referring to community-based rheumatologists who spend most of their time doing primary care, or are we focusing on academic cardiovascular surgeons who have less to do because of the success of primary care physicians in reducing the prevalence of coronary heart disease?

This raises an important point: Specialists will not change their practice to primary care until the suspected or actual threat of income loss becomes such that they feel there is little choice left.[3]

Definitions

Before taking a position on whether specialists will become generalists, let us define some terms.[6,7]

Primary care includes family physicians, general internists, and general pediatricians. These physicians

> are specifically trained to provide first contact, coordinated, comprehensive, and continuous care to persons with a broad range of health concerns not limited by problem origin, gender, organ system or diagnosis. Primary care includes the management of acute and chronic illness, preventive services, counseling and prevention.[7(p261)]

Subspecialists—medical or surgical—are not trained in these generalist disciplines. The scope of their practice is "in some way limited to or focused on a particular disease process, condition or organ system or on the use of specific technological interventions."[7(p261)]

Background

Currently, only a third of allopathic physicians in the United States are practicing generalists. Just 30 years ago this figure was 50%, and 60 years ago it was 90%.

More troublesome is the fact that in 1982, more than a third of our medical school graduates went into primary care fields—14% in general medicine and 15% in family practice, with the remainder in pediatrics—whereas in 1993 only 15% said they plan to enter a primary care field—3% in general medicine, 3% in pediatrics, and 9% in family practice.[9] Why is this? In 1993 the Association of American Medical Colleges appointed a Task Force on the Generalist. This group administered a questionnaire to a large number of graduating medical students to find out the reasons for certain career choices. Let us look at their findings.[10]

- *Practice demographics.* In general medicine, patients seek care with undifferentiated problems. They are often elderly and frequently have chronic illness or psychosocial problems, or both. Recently an increasing number of patients have problems related to the human immunodeficiency virus. Many patients have relatively straightforward, self-limited, even mundane illnesses.[3] Primary care physicians value continuity of care and are interested in psychosocial issues. They are reasonably comfortable making decisions based on vague probabilities. Those attracted to specialty fields desire tangible and immediate results and prefer more certainty in their therapeutic decision making.
- *Intellectual content of the field.* Generalists must be comfortable with a large, ever-changing body of knowledge. This is often intimidating to the specialty-bound students and residents who prefer a limited information base that they can master comfortably.[11]
- *Lifestyle.* Because specialists are able to make more money in a shorter period of time, those entering fields with controllable lifestyles—anesthesia, radiology, dermatology, emergency medicine, and many of the surgical subspecialties—often work a third to half the number of hours per week that a primary care physician does, and in so doing make a substantially higher income.[10,11]
- *Debt burden and finances.*[11-15] The average debt of today's graduating medical student is $46,000. It is $75,000 if the student graduates from a private medical school. To comfortably repay a debt of $75,000 within five years requires an annual income of $145,000. If the debt is $120,000 (which is becoming more frequent), the

(Jacobs M: Can the specialist be a generalist? West J Med 1995; 162:68-70)

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physician would need an annual income of $266,000 to repay this amount within the same time period.

The median income of a general internist is about $112,000; of a gastroenterologist, $186,000; of a radiologist and anesthesiologist, $300,000; and of a cardiovascular surgeon it is $441,000. For every 1% increase in anticipated income, the number of students choosing that specialty increases by 0.5%.[15] If a specialist has been in practice several years, expenses or debt burden will be in equilibrium with income, and it would be painful indeed to adjust to today's primary care physician's salary.

• *Personality factors and prestige.*[10-12] This is a common reason given for a specific career choice: a specialty is chosen that is thought to be appropriate to a student's temperament and personality. This reflects, in a complex way, a mixture of aversions and attractions to the actual and apparent attributes of the various specialties. Here the perception of the prestige of the field plays an important role and is determined both by patient attitudes and those of the faculty who taught the student.

Practical Considerations

Assuming that there are specialists who really do wish to (or have to) retool to be primary care physicians, who will pay for the retraining, define the core competence, and issue credentials for the training programs and the trainees?[7] No guidelines exist for retraining specialists to become generalists, and this becomes even more complicated given the wide variety of specialty types. Resolving these issues is important because in the reformed health care system, reimbursement for primary care will be linked to demonstrable or certifiable competence in this area.

There are four possible ways to do this[7]:

• *Formal board certification.* A specialist would reenter an existing primary care training program, in all likelihood with a year's credit given for the advanced training that specialists have already had in their field. This would be a costly option, both in time and money.

• *An organizational certificate of qualification.* Specialists could use functioning primary care residency programs for their clinical practice and supervision, but in a less intense way than in the first option. A graduate of this program would then be certified by an existing organization such as the American Council of Graduate Medical Education. Again, this would require a major investment of time and money.

• *An institutional certificate of completion.* A specific institution may choose to retrain its own specialists and issue a site-specific certificate of completion. This likely would be the continuing medical education model most attractive to practicing subspecialists desiring a career change. The problems here have to do with a lack of standard curricula and an unclear meaning of a certificate of completion outside the sponsoring institution.

• *Primary care apprenticeship.* A subspecialist would simply shadow a certified generalist until both thought that the specialist was competent to function alone. Variability of experience and lack of quality control are clear drawbacks to this option.

The Answer

Professionals are determined by their knowledge, skills, attitudes, and behaviors. Any specialist could readily learn the knowledge and skills of a generalist, but retraining would definitely be necessary. But what about the attitudes and behaviors that determine satisfaction of both physicians and patients and effectiveness? Would specialists enjoy seeing the types of patients generalists see, and would they be sufficiently motivated to remain current and skilled in this field? Would they tolerate the necessary continuous availability to their patients? Would they practice the necessary cost-effective care required in a managed care system? Data exist that suggest that specialists' care for the same type of patient is more expensive than that of generalists.[16]

I think that attitudes that determine the original decision to enter the specialist's chosen field are deep-seated—not immutable, but close to it. So for me, the answer to whether specialists can become generalists is this: Except under special circumstances, the priest and the rabbi should stick to their chosen religions; the football player and ballet star should remain on the field and the stage, respectively; and the specialist and generalist should continue to do what they love and do the best.

Postscript

In all likelihood, special circumstances will prevail. The relentless growth of managed care will continue; more care will be provided by generalists in partnership with physician-extenders; and the subspecialist, both community and university-based, will be faced with a dwindling source of patients. What advice is there for these committed and hard-working physicians? Certifying competency eventually will be required. Until then, I suggest the following, especially applicable to subspecialists who have limited their practices to a narrow field:

• Change is always difficult, abrupt change more so than gradual. Anticipate this and make the necessary practice transitions sooner rather than later. If given a choice, sign on with managed care organizations as a primary care physician rather than as a subspecialist;

• Trepidation about the unfamiliar is natural. Broadening exposure to primary care problems will lead to increased comfort (enjoyment?) with this discipline;

• We avoid that which makes us feel inadequate. Learn about dizziness, headaches, back pain, functional bowel disorders, and the like. Having this framework when seeing patients with mundane, self-limited, and stress-related problems promotes confidence, and from this sense of competence professional satisfaction will likely follow;

• Try to consciously change the goal of encounters with patients from a need for a definitive diagnosis and treatment to an understanding of the human condition and the value of the therapeutic relationship. This is the

underpinning of the effectiveness of a generalist and may be the most difficult adjustment to make;

- Associate with those generalist colleagues who relish the excitement of general internal medicine, who thoroughly enjoy the daily challenges of solving the myriad of undifferentiated medical problems that they see. Attend their conferences. Freely and frequently discuss patients with them; and
- Do not neglect that which sustained you intellectually and professionally for many years. Continue to provide consultations in your area of expertise. Attend subspecialty conferences and, time permitting, teach on university consultation services and in the clinics.

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Radiologic Case

Right Hilar Mass

WILLIAM O. BERLIN, MD; HOWARD LEVY, MD; DOUGLAS W. MAPEL, MD; *and*
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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 61-year-old man was admitted to the hospital with a history of shortness of breath for 2 weeks. He had smoked one pack of cigarettes per day for more than 40 years, but had stopped smoking during the week before admission because of cough and shortness of breath.

On physical examination, he was thin, but appeared to be in good health. Posteroanterior and lateral chest x-ray films were taken (Figures 1 and 2). What is the differential diagnosis, and what is the most likely possibility? What imaging test would provide the most information about the process?

What is the most likely diagnosis in this patient?

How would you confirm the diagnosis?

What other test would you do?

How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

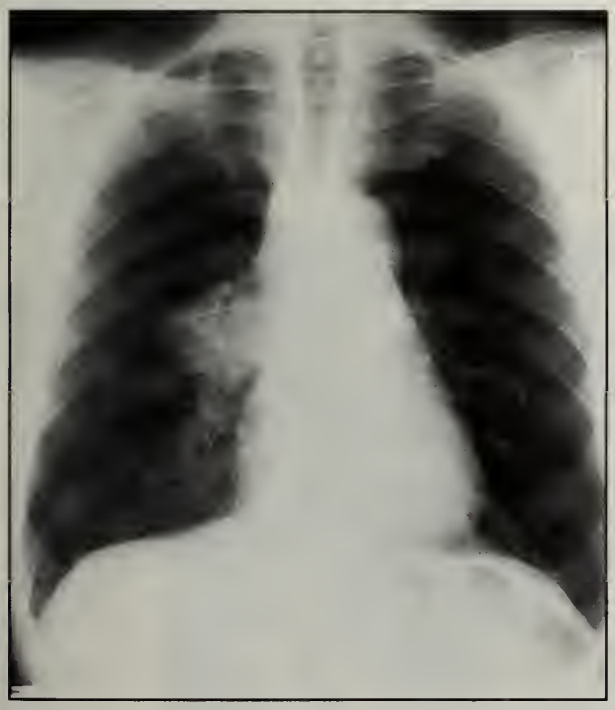

Figure 1.—A posteroanterior chest x-ray film shows an obvious right hilar mass.

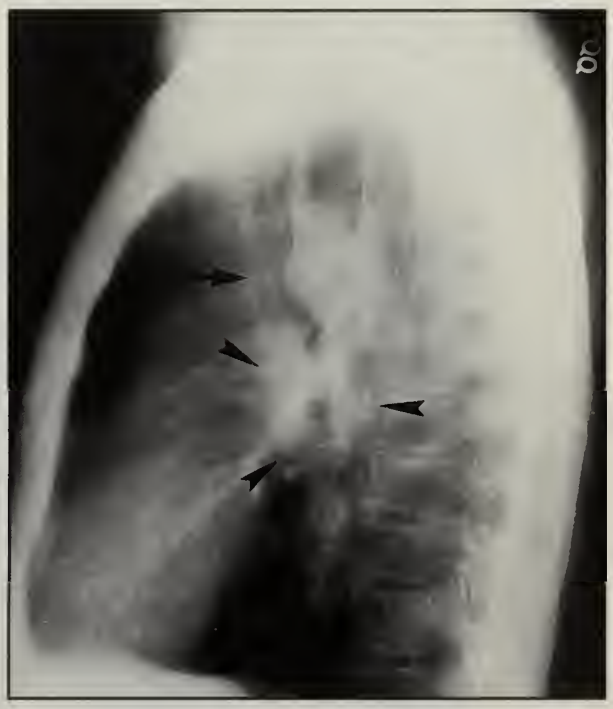

Figure 2.—A lateral chest x-ray film shows the right hilar mass (**arrow heads**). A second, mediastinal mass can be seen indenting the posterior wall of the trachea (**arrow**).

(Berlin WO, Levy H, Mapel DW, Manley J: Right hilar mass. West J Med 1995; 162:71-72)

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ANSWER: Squamous cell carcinoma of the esophagus with hilar metastasis

Comparison of the postanterior and lateral chest films shows that the obvious right hilar mass is superimposed on the bronchus on the lateral film (Figure 2). There is another mass above the hilum, which can be seen impinging on the posterior wall of the trachea. These findings could be due to primary lung carcinoma with metastasis, nonthoracic malignancy with metastasis to both the hilum and mediastinum, or to a primary mediastinal lesion with spread to the lung.

The computed tomographic (CT) scan (Figure 3) shows a circumferential mass involving the esophagus and extending into the posterior wall of the trachea. Scans at other levels showed the right hilar mass. No pulmonary mass was present. While pulmonary carcinomas and metastases from other organs often involve mediastinal nodes, a circumferential mass around the esophagus strongly suggests that this is the origin of the malignancy. The CT findings led to endoscopic examination and biopsy, which confirmed the diagnosis.

Malignant esophageal neoplasms constitute 7% of gastrointestinal tumors. Squamous cell carcinoma is the most frequent neoplasm of the esophagus and represents 90% of all esophageal cancers. This lesion has been linked to conditions causing injury to the esophageal mucosa, particularly smoking and ethanol intake. Other environmental risk factors have been less clearly defined, but some of these are also thought to play a role.

On histologic examination, there is variability of the pattern of tumor growth and level of differentiation, but these factors are of little prognostic value. Direct invasion by or lymphatic spread of the tumor, or both, may involve any contiguous structure. As much as 40% of esophageal neoplasms arise in the middle third of the esophagus, and lymphatic spread of the tumor from this region is predominantly to the mediastinum. The tumor will then present as hilar adenopathy or mediastinal mass, as in this patient.

Presenting symptoms, although most often indicative of esophageal disease and systemic illness, may include respiratory symptoms of cough due to bronchial irritation, hoarseness with recurrent laryngeal nerve involvement, pneumonia from aspiration or bronchial obstruction, hemoptysis, lung mass, or aspiration due to tracheobronchial fistula. A careful history should be taken for the presence of esophageal disease in patients with these symptoms.

Computed tomography and magnetic resonance imaging are both useful tools in the evaluation of mediastinal masses. They provide information about metastasis, extrapulmonary extension, staging, and resectability. Bronchoscopy is necessary to evaluate pulmonary involvement. Percutaneous biopsy can be accomplished with CT guidance in lesions not amenable to endoscopic or fluoroscopic biopsy. In this patient, demonstration of the tracheal involvement documented the unresectability of the tumor and directed therapy toward palliation. The prognosis is poor in all patients with esophageal carcinoma. Even patients with limited disease who are subjected to aggressive treatment have five-year survival rates of 4% or less.

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Figure 3.—A computed tomographic scan at the level of the mediastinal mass shows circumferential involvement of the esophagus (**arrow**) and protrusion into the posterior wall of the trachea.

Editorials

Dizziness in Primary Care

NEXT TO FATIGUE, dizziness may be the most common nonpain physical complaint seen in primary care. Yet, like fatigue, dizziness remains a diagnostic and therapeutic gadfly. It is the rare clinician or student of medicine who exclaims to colleagues, "Let me tell you about a great case of dizziness I've just seen." Our insecure approach to this intangible symptom does not breed much enthusiasm. The review by McGee in this issue of the journal[1] complements nicely several recent reviews[2,3] and is both a practical starting point for primary care physicians and a springboard from which to point out some good news, some shaky conventional wisdom, some preliminary advice, and some directions for future research.

Prognosis is the good news. In a recent study of 100 primary care patients with a chief complaint of dizziness, serious cardiovascular or central nervous system causes were not apparent initially,[4] nor did they develop over a one-year follow-up period.[5] Moreover, a third of patients symptomatically improved within the first several weeks and another third gradually got better over the next 4 to 12 months. Follow-up rather than an expensive workup may suffice as the initial approach for many dizzy patients.

Diagnosis and therapy represent the shaky ground. Certain assumptions about dizziness deserve to be challenged. First, is cerebrovascular disease an important cause? Although a stroke or transient ischemic attack arising in the posterior circulation is a commonly entertained diagnosis in elderly patients, the few retrospective studies conducted in hospital or referral settings cited by McGee and elsewhere do not establish the frequency of "vascular vertigo."[1,6] Transient ischemic attacks are entirely a clinical diagnosis, and because there is no definitive treatment of posterior circulation ischemia, their association with isolated dizziness is particularly difficult to prove. While preliminary studies suggest that dizziness in the absence of other neurologic symptoms seldom represents an ischemic event in primary care,[5,7,8] the true incidence of cerebrovascular dizziness is unknown.

Second, what about hyperventilation? Although Drachman and Hart reported that nearly one in four cases of dizziness could be attributed to hyperventilation,[9] patients experiencing symptoms with this maneuver in a recent study almost always had another etiologic explanation, most commonly a vestibulopathy or psychiatric disorder.[4] Furthermore, their dizziness was reproducible, on average, by at least two other maneuvers, suggesting that hyperventilation may be a nonspecific provocative maneuver in suggestible or sensitive patients.

Third, what about cardiac arrhythmias, Meniere's disease, acoustic neuromas, labyrinthitis, and other specific causes? These in fact account for few cases. Other than the common and discrete disorder of benign positional vertigo, most dizziness is not nosologically crisp but rather vertiginous, psychiatric, idiopathic, or multicausal in nature. Whereas vertigo and psychiatric disorders account for two thirds of cases, most vertigo (except for benign positional vertigo) can at best be characterized as peripheral or central, and psychogenic dizziness has not yet been put to the therapeutic test. In fact, lack of specific therapies for many types of dizziness is one of the Achilles' heels in our ability to confidently ascribe etiologic labels. Other limitations include the difficulty patients have in precisely describing their dizziness and the lack of objective and agreed-on diagnostic tests. All of these factors explain the considerable disagreement even among experts about the cause of dizziness in individual patients.[4]

Fourth, what about the role of meclizine in treating dizzy patients? Although it may have a palliative role in acute vertiginous attacks lasting hours or days, such as labyrinthitis and Meniere's disease, it is widely prescribed for patients with many other types of dizziness. The episodes of benign positional vertigo are too brief to warrant drug therapy and are better treated with habituation exercises.[2] Nonspecific peripheral and central vestibulopathies are the cause of dizziness in more than half of patients with vertigo and often produce sporadic and self-limited spells for which long-term drug therapy may not be indicated or effective. The strongest studies supporting the use of meclizine, other antihistamines, and anticholinergic medications involve motion-sickness prevention and thus cannot be readily generalized to the treatment of patients with dizziness. The several small studies cited by McGee as showing a beneficial response of dizziness to meclizine use were of short duration and involved only small numbers of patients.

What should be the primary care approach to the dizzy patient? A focused history and physical examination is the most valuable diagnostic tool, and even here detailed cardiac and neurologic examination has a low yield. The most useful historical information is patients' own descriptions of their dizziness, its characterization as "spinning, fainting, or falling" (that is, vertigo, presyncope, or disequilibrium), and the effects of position (lying down, standing, walking) on patients' symptoms. The most useful physical examination maneuvers are the Hallpike (head-hanging) test for benign positional vertigo, supine and standing blood pressure and pulse measurements to detect orthostatic changes, and observing the patient walking across the room, turning around, and walking back. Also, the physician can do a one-minute bedside vestibular examination looking for nystagmus present in the primary position, with eccentric gaze, and after rebound and head-shaking.

Routine laboratory testing, electrocardiography, and audiometry are seldom helpful. Expensive tests such as neuroimaging and ambulatory cardiac monitoring also have a low yield and can be reserved for patients with other indications of neurologic or cardiac disease. For patients with persistent dizziness, vestibular testing and

evaluating for psychiatric disorders are the two most useful steps. Because depression, anxiety, and somatization are the most common psychiatric disorders associated with dizziness, these can often be evaluated and even treated by a primary care physician, referring only the more severe or refractory cases to a mental health specialist. Various types of vestibular testing, including electronystagmography, rotatory chair, dynamic posturography, and clinical evaluation, can be done by a neuro-ophthalmologist or neuro-otologist. Whether any one of these tests is superior to the others or how often such testing actually changes patient management is unclear.

Dizziness is rife with questions for primary care researchers. Does dizziness associated with treatable psychiatric disorders such as depression and anxiety respond to psychotropic medication or psychotherapy? Can dizziness attributable to a chronic vestibulopathy improve with vestibular rehabilitation, or is it an irreversible symptom that must be tolerated, in the words of Jonathan Swift, "That old vertigo in his head/Will never leave him till he's dead"? One positive study of vestibular rehabilitation showed relatively modest and inconclusive benefits.[10] Is one type of vestibular testing superior to another, and does such testing make a difference in clinical management and patient outcome? What is the role of subspecialists, such as neurologists and otolaryngologists, in the care of dizzy patients, and which patients benefit from referral? Can we reduce the amount of laboratory testing, neuroimaging, and other low-yield tests without adversely affecting patient outcome? Are meclizine, other antihistamines, and anticholinergic medications beneficial in any type of dizziness other than acute and prolonged vertiginous attacks? While the disorder often resolves, its persistence in a considerable minority of patients causes substantial suffering and functional impairment.[11] As a physical symptom for which patients' self-reporting is the gold standard, dizziness will always be difficult to study, and our research findings will have rougher edges than in many other areas of clinical investigation. But as long as dizziness crosses the clinic threshold as often as it does—10 million visits annually in the United States alone—imperfect answers that are even a slight improvement over previous imperfections are worth the investment.

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Surfactant Replacement Therapy—Room for Improvement

WE BREATHE EFFORTLESSLY because of pulmonary surfactant. Unfortunately, very premature infants lack surfactant and have labored breathing and respiratory insufficiency. Medical conditions associated with alveolar instability and microatelectasis are prime candidates for surfactant replacement therapy. Surfactant replacement therapy for preventing and treating the respiratory distress syndrome in newborns is a major therapeutic advance in neonatal care and is comprehensively reviewed by Poulain and Clements elsewhere in this issue.[1] Pulmonary surface-active material is composed of phospholipid, cholesterol, and associated surfactant proteins, which are designated SP-A, SP-B, and SP-C.[2] There is a fourth surfactant-associated protein, SP-D, that binds to surfactant weakly and is physiologically a host-defense molecule.[3] Surfactant is synthesized by alveolar type II cells and packaged in lamellar inclusion bodies. After secretion by endocytosis, this material unravels to form tubular myelin, a unique physical form of surfactant, and then adsorbs to the air-liquid interface. Surfactant proteins A and B are necessary for the formation of tubular myelin. They organize the three-dimensional structure of the phospholipids. Adsorption occurs during inhalation when the surface film is expanded, and during exhalation a low surface tension is formed when the surface film is compressed. After repeated respiratory cycles, some of the lipids of surfactant are squeezed from the air-liquid interface, enter the subphase, and are endocytosed by type II cells for reuse. The uptake of extracellular surfactant by type II cells is facilitated by SP-A.

The development of surfactant for replacement therapy underscores the importance of basic science in providing a framework for clinical science. The initial physiologic studies that showed that a low surface tension was present at the air-liquid interface in the lung was reported by von Neergard in 1929. This observation was not widely appreciated, however, and had to be rediscovered in the 1950s. At that time Pattle and Clements independently isolated and identified surfactant as the substance that produced the low surface tension in the lung and defined its physical properties.[4,5] This basic science precept was then rapidly applied to a clinical situation. Within three years surfactant was reported to be deficient in the lungs of infants who died of hyaline membrane disease.[6]

Soon the unusual phospholipid that was responsible

for the low surface tension, dipalmitoyl phosphatidylcholine (DPPC), was identified in surfactant. The logical next step was to administer DPPC to infants with the respiratory distress syndrome, and this was accomplished in the early 1960s. The clinical trial with liposomes of DPPC failed, however.[7] In retrospect, the trial failed because the critical importance of the adsorption of DPPC to the air-liquid interface was not appreciated at the time. Later it was found that the proteins of surfactant or other amphipathic molecules such as long-chain alcohols were necessary for the rapid adsorption of surfactant to the surface film. Dipalmitoyl phosphatidylcholine by itself adsorbs to an air-liquid interface over hours, but adding unsaturated phospholipids and the surfactant proteins can speed the adsorption rate to seconds. If our breathing rate is 12 times per minute, adsorption must occur within a few seconds to provide the low surface tension at the end of the next exhalation.

There is no doubt that the preparations of surfactant for replacement can be improved. Current studies on the structure-functions relationship of the surfactant proteins will lead to a better understanding of how they regulate phospholipid organization and movement at the air-liquid interface and ultimately to the next generation of surfactant formulations for replacement therapy. Basic science has led to a better understanding of the role of surfactant proteins on phospholipid trafficking in the alveolus and provided reagents for diagnosing new diseases. For example, a subset of infants with respiratory distress has been shown to be deficient in surfactant protein B.[8,9] Likely genetic variants in the other surfactant proteins will be discovered in the next few years. Tools will become available for gene therapy and new modes of therapy using the surfactant proteins or genes to express them over the next decade.

The surfactants that are currently used for replacement therapy can be divided into two groups. The group designated natural surfactants comprises extracts of minced lung or pulmonary lavage and includes the two hydrophobic surfactant proteins, SP-B and SP-C. The other group, the artificial surfactants, does not contain these proteins. Soon there will be additional surfactant preparations that will contain synthetic peptides or modified recombinant proteins that mimic the natural proteins. In animals born prematurely or with acute lung injury, natural surfactants appear to have physiologic advantage over the current synthetic surfactants.[10] Superior clinical efficacy in direct comparison has not been demonstrated to date.

Surfactant replacement therapy for the prevention and treatment of the respiratory distress syndrome in newborns has changed the care of premature infants and has shown the need for early, prompt therapy.[11] Although prophylactic treatment of very small infants is most effective, treatment after the respiratory distress begins (rescue therapy) is nearly as effective. In either case, there is a reduction in mortality and in the incidence of pneumothoraces or air leak presumably due to reduced airway pressures during mechanical ventilation. There is no decrease in the incidence of intraventricular hemorrhage or the number of babies in whom bronchopulmonary dysplasia develops. There also is no increase in the number of babies with bronchopulmonary dysplasia, as might be envisioned if the treatment were only slightly effective. Initially there was concern that the treatment, if successful, would produce a large cohort of severely handicapped babies. This has not occurred, but the survivors do show substantial physical impairment and learning disabilities, and there is room for an improved outcome.[12]

Surfactant replacement therapy for other diseases is just beginning. Surfactant dysfunction plays an important role in the pulmonary manifestation of the adult respiratory distress syndrome (ARDS). This fact was clearly recognized at the time the syndrome was designated.[13] Surfactant recovered from patients with ARDS is abnormal in its ability to lower surface tension and composition.[14,15] Studies of surfactant replacement therapy in patients with ARDS are still in the pilot stage; surfactant replacement will likely improve pulmonary compliance and gas exchange.[16,17] Further studies will be needed to show the role of surfactant replacement therapy on mortality, the prevention of the extrapulmonary manifestations of ARDS, and the development of chronic lung disease.

Surfactant is not restricted to the alveolar spaces, but is also found in small airways. Enhorning and Holm have developed a theoretical and physiologic rationale for the important role of surfactant in small airways.[18] Surfactant is needed to prevent small airway collapse and for high pressure to open liquid-filled airways. In addition, by immunocytochemistry and in situ hybridization, the nonciliated bronchiolar cells of rodents express the surfactant proteins A, B, and D. The precise function of these proteins in small airways is not known, but a likely function for SP-A and SP-B is in the movement and organization of surfactant in small airways. Although definitive clinical studies have not been reported, it is certainly possible that exogenous surfactant will find a place in the treatment of acute severe asthma.

Improvement in the treatment of ARDS and bronchopulmonary dysplasia will likely require the addition of other pharmacologic agents. Surfactant can stabilize the alveoli and may prevent the loss of gas-exchange units by lessening the apposition and fusing of atelectatic denuded alveolar walls. This will do little to repair damaged epithelium or clear the alveolar exudate, however. One of the critical features of acute lung injury is the loss of many alveolar type I cells, the flat squamous cells that cover most of the alveolar wall. In wound healing, the epithelium must be restored to prevent the outgrowth of fibroblasts. This would be facilitated by exogenous growth factors, especially growth factors that stimulate epithelial proliferation but not mesenchymal cell proliferation such as keratinocyte growth factor.[19] After the alveolar epithelium is reestablished, treatment could focus on stimulating the transport of fluid from the

alveolar space into the interstitium. Transepithelial transport can be stimulated by β-adrenergic agents and can increase the rate of clearance of pulmonary edema when the alveolar epithelium is intact.[20]

Exogenous surfactant has additional possible pharmacologic uses. It could be useful for delivering lipophilic drugs such as cyclosporine for patients with lung transplants. Finally, because SP-A binds to alveolar type II cells and stimulates endocytosis, it may be useful to target vectors for gene therapy for the alveolar epithelium. A vector with SP-A protein as an external ligand could theoretically be used to target the SP-B gene to type II cells in infants whose respiratory distress syndrome is caused by a lack of SP-B.[9]

Acknowledgment

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Echocardiography

To the Editor: In a recent article by Chou and Amidon regarding the noninvasive evaluation of patients for coronary artery disease,[1] the authors recommended radionuclide scintigraphy with exercise or pharmacologic stress in patients with abnormal baseline electrocardiogram results, suspected false-positive exercise treadmill test results, or the inability to exercise. Stress echocardiography is relegated to patients with poor tolerance for exercise or severe airway disease, or both.

Stress echocardiography is a well-validated modality with more than 15 years of published data in the noninvasive evaluation of coronary artery disease. We concur with the authors' comment that the test is operator dependent but would add that this also applies to radionuclide scintigraphy to the same extent. As stated in the article, stress echocardiography is as sensitive and specific as stress radionuclide scintigraphy, both for pharmacologic stress and exercise. We would like to point out the following advantages of stress echocardiography versus radionuclide scintigraphy:

- Echocardiography provides information regarding ventricular contraction, chamber dimensions, and valvular function. Echocardiography is unique in the ability to detect occult critical aortic stenosis, a lesion commonly regarded as a contraindication to any stress study. Other causes for exercise intolerance are also established, such as mitral valve disease or pulmonary hypertension. These diagnoses cannot be made by radionuclide scintigraphy;
- Rapid performance and interpretation, typically in 60 minutes or less compared with four hours or more of delayed views and image processing for radionuclide scintigraphy studies;
- Similar ability as radionuclide scintigraphy to detect hibernating myocardium using dobutamine echocardiography;
- Favorable cost profile compared with radionuclide scintigraphy—stress echo is a third to a half the cost of radionuclide scintigraphy. In the era of cost containment, this reason alone should be sufficient;
- Stress echo does not involve any radiation; and
- Exercise echo is noninvasive and does not require any intravenous access.

With the added benefits of stress echocardiography over radionuclide scintigraphy, it is unclear to us why Chou and Amidon recommend radionuclide scintigraphy as the test of choice for the multiple scenarios listed in their article.

We suggest that stress echocardiography should be the first noninvasive test done for many patients for the diagnosis and assessment of coronary artery disease in view of its superior accuracy over treadmill electrocardiography and its many advantages over radionuclide scintigraphy.

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* * *

Drs Amidon and Chou Respond

To the Editor: Drs Abdullah and Pollick make many valid and appropriate points. They comment that echocardiography provides additional information, including ventricular and valvular function. They also note that echocardiography can be done rapidly and does not involve radiation. We agree with all of these points and mentioned them in our article. In centers that have expertise in doing exercise echocardiography and in patients whose echocardiographic images are of good quality, stress echocardiography is a viable alternative to stress scintigraphic imaging.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

On Being a Physician

NANCY L. GREENGOLD, MD, *Los Angeles, California*

I thought I had become a physician in my second year of residency, repleting potassium by telephone, assessing a patient's status from hemodynamic data, diagnosing arrhythmias from a monitor strip. I talked with confidence, inspiring awe in the poor interns who struggled to remember the mnemonic for anion gaps. My talent, I thought, was projecting control. Never let them see you sweat.

This year, as I became a third-year resident, prepared for more of the same, I got a rude surprise. Our department of medicine announced an experiment in cost containment involving the hematology-oncology rotation—by halving the number of house staff used to cover the same service in previous years. Residents would now function again as interns on their on-call nights. Back to the frontline. I was incredulous. Draw blood specimens to culture for fever spikes? What an insult! What a waste of my intellectual talents, when I could be copying review articles for my intern in the library! I dreaded the anticipated month of "Hem-Onc" for weeks in advance.

On the first day of the rotation, I split up with my counterpart resident the number of patients previously handled by four teams. To divide up the probable "rocks," patients who stay "forever" for chemotherapy runs, we agreed to accept a system of random selection of the index cards containing the names and bleak histories of all the patients on the ward. There were a few women with end-stage ovarian cancer, a man with multiple myeloma, and a patient with a newly diagnosed leukemia who had come in the night before. His deal, my pick.

I got the new patient with leukemia, room 4918, a woman in her 20s, cut down 24 hours earlier by a phone call ordering her to the hospital immediately.

She had reported headaches for a week; she recalled that at first her physician had flippantly suggested that she see a masseuse, attributing her symptoms to her high-stress job in business. She returned to his office seven days later, unable to stand the pain, defending herself to him: "I don't like to complain, but this isn't my usual tension headache." He took some blood. The report of a white blood cell count of 134,000 came back the next day, and she received the terrifying phone call at work.

The patient was sitting up in bed calmly, with a physiognomy that defied a diagnosis of cancer. She was wildly attractive with the glow of one in the prime of health. Her wide palpebral fissures were the only hint that a nightmare frayed at the edges of her soul.

Initially she would not cry in front of me, protecting her anxious parents at her bedside. "I really don't have time for this," she giggled reflexively. "I just landed a big client in Hollywood. I'm only 24, and I've got a lot of responsibility. I wouldn't be surprised if this whole thing turned out to be stress related."

There must be some mistake, Doctor, her eyes pleaded. The patient's siblings were physicians, but, try as they might, their influence bought her nothing more than the promise of a sleeping pill at night. They could not alter the white blood count.

On admission, she had been given the diagnosis by her newly appointed oncologist, along with an outline of the immediate treatment plan and a suggestion that her future might include a bone marrow transplant if a match could be found. She took it stoically. On the first day we met, I asked her to tell me her understanding of the diagnosis, and she repeated clearly, "Well, I have this thing called CML, and we're working to lower my WBCs. And I have to think positively. Say, do you think I'll be able to take a trip overseas in December? My family has been planning it for so long."

I did not provide any unsolicited information that day. But two days later, I got an urgent call from her nurse. When I arrived, the patient looked angry. Her mother was sniffling beside the bed. "Doctor, I need some answers," demanded the patient. "First, what is an oncologist?"

"A cancer specialist," I replied, sitting on the edge of her bed.

"Do I have cancer?" she asked.

"Yes, you have leukemia."

"I do?" she stammered. All she remembered being told was "CML," the sugar-coated acronym supplied by the oncologist along with the hydroxyurea pills.

As the anguish poured forth gutturally from her throat, the sense of her horror became mine. I thought of how a diagnosis like this would crush my parents—their genetic

(Greengold NL: On being a physician. West J Med 1995; 162:78-79)

Dr Greengold is a third-year resident at Cedars-Sinai Medical Center in Los Angeles, California.
Reprint requests to Nancy L. Greengold, MD, 135 N Swall Dr, Apt 306, Los Angeles, CA 90048.

wonder contaminated by cancer, their years of giving and protecting all coming down to this. Would they now be witness to my painful act of dying rather than vice versa, as tradition entails? Would they have to stand by helplessly watching the thick, curly locks fall from grace, the eyes hollow out, the gaunt concentration-camp facies develop?

The patient grabbed at her beautiful hair, miming the dreaded question to me as she raised the specter of chemotherapy. As I nodded reluctantly, the tears swelled over the banks of her arched cheekbones. The flood of pestilence washed over me as I sat with mother and daughter confronting the shock, the injustice of random selection. We spoke about the devastated father, unable any longer to come to the hospital for fear his daughter would see him cry. We spoke of the burden of loving.

I remained in the room with no medicine to offer but my presence. I still wore my physician garb, but my arrogance was gone. Though I wanted to be a dispassionate sounding board, I could not. She needed a small speck of hope, even small lies, to get her through the night. She needed my hand. She needed my time, even as my relentless beeper sought my attention for nurses reporting falling hematocrits and low potassiums. I stayed with my patient.

As I sat with her, I wondered. Had I forgotten what a physician was during my cavalier days as a second-year resident, managing the service from a computer terminal? Had I forgotten that "CML" is not a Philadelphia chromosome gone awry, but three awesome letters wreaking havoc on a young woman untimely ripped from life? Back in the trenches of internship, perched at the bedside of my patient, her nails digging into my hand, no electrolytes to calculate, no orders to write, I found I had become a physician again.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

Poems

APHIDS IN THE ROSE

Today, trying with a damp Q-tip
to swipe the aphids off the rosebush,
I wonder what concussion has occurred
inside my body, which cell it was
that woke up one morning with its RNA
gone nuts, a crazed terrorist
who tortures himself.
The doctor confirmed earlier reports
of inexplicable madness, my cervix
giving in to strange demands:
shoes on backwards, hands waving out of ears,
whole neighborhoods of nuclei
dancing maniacally.
I had seen pictures of cells
undergoing their dignified divisions—
rows of identical platoons
splitting their heads in half—
and then, for no apparent reason,
the sergeant shouts the right words
in the wrong order, his error
rippling through ranks, undeciphered.
Meanwhile, citizens are fleeing the cities
with wounds that can kill them,
something like napalm or radioactive tissue.
The whole womb-neck may as well
be a Bikini Island.
The doctor says my best hope is to
burn the thing down below ground level,
the deeper the better.
She's one of those who knows
the good effects of death.
I'm still poking at these flimsy aphids,
arguing against myself,
wincing at each surrender.

JOAN BARANOW©
Mill Valley, California

WHITE RABBIT II

Alice is not here today
But the Hatter just ran through
My ears seem long and furry
And my eyes are awfully pink
The hand which holds my pocket watch
Is looking very strange
I'm feeling most peculiar
But the waiting room is full
The usual conglomerate
But just a little odd
Mrs. Smith has faded out again
Leaving just a grin
The Whitlow twins are looking round
They're singing "Tweedle, Tweedle"
There's a hedgehog sitting on a chair
Reading last week's *People*
My office nurse is screaming
I think, "Off with his head"
The toadstool in the corner
Wasn't there when last I looked
My notes are all in Jaberwock
I can't make out a word
My whiskers are all quivery
And time is running out
I'll never get through rounds today
I'm late, I'm late, I'm late!

CATHARINE T. CLARK-SAYLES, MD©
Mill Valley, California

In Memoriam

California Medical Association

Beretta, Franco, Oakland. Died Aug 27, 1994, aged 73. Graduate of University of Washington School of Medicine, Seattle, 1950. Licensed in California in 1955. Dr Beretta was a member of the Alameda-Contra Costa Medical Association.

Bernstein, Abraham, San Francisco. Died Sep 7, 1994, aged 91. Graduate of University of California, San Francisco, School of Medicine, 1927. Licensed in California in 1927. Dr Bernstein was a member of the San Francisco Medical Society.

Branson, Allan Bruce, Sacramento. Died Oct 25, 1994, aged 71. Graduate of University of California, San Francisco, School of Medicine, 1954. Licensed in California in 1955. Dr Branson was a member of the Sacramento-El Dorado Medical Society.

Carson, James G. Jr, Napa. Died Nov 26, 1994, aged 63. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1956. Licensed in California in 1957. Dr Carson was a member of the Napa County Medical Society.

Cho, Michael M., Placentia. Died Oct 23, 1994, aged 47. Graduate of College of Medicine, Catholic University, Seoul, 1970. Licensed in California in 1974. Dr Cho was a member of the Orange County Medical Association.

Clark, Dan W., San Jose. Died Oct 31, 1994, aged 69. Graduate of Stanford University School of Medicine, Stanford, California, 1950. Licensed in California in 1951. Dr Clark was a member of the Santa Clara County Medical Association.

Fassett, James R., Gonzales. Died Nov 6, 1994, aged 74. Graduate of Stanford University School of Medicine, Stanford, California, 1945. Licensed in California in 1946. Dr Fassett was a member of the Monterey County Medical Society.

Fink, Michael John, Loma Linda. Died Oct 17, 1994, aged 30. Graduate of Baylor College of Medicine, Houston, Texas, 1991. Licensed in California in 1992. Dr Fink was a member of the San Bernardino County Medical Society.

Gordon, William E, San Luis Obispo. Died Dec 4, 1994, aged 73. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1947. Licensed in California in 1969. Dr Gordon was a member of the San Luis Obispo County Medical Society.

Grandi, Joseph, San Jose. Died Nov 29, 1994, aged 78. Graduate of New York Medical College, New York, 1943. Licensed in California in 1955. Dr Grandi was a member of the Santa Clara County Medical Association.

Hom, Paul Francis, Sacramento. Died Nov 5, 1994, aged 53. Graduate of University of California, Davis, School of Medicine, 1973. Licensed in California in 1974. Dr Hom was a member of the Sacramento-El Dorado Medical Society.

Kmak, Frank J., Daly City. Died Nov 25, 1994, aged 63. Graduate of Indiana University School of Medicine, Indianapolis, 1955. Licensed in California in 1959. Dr Kmak was a member of the San Francisco Medical Society.

Moore, Dan Burdette, Sacramento. Died Nov 10, 1994, aged 65. Graduate of Washington University School of Medicine, St Louis, Missouri, 1955. Licensed in California in 1972. Dr Moore was a member of the Sacramento-El Dorado Medical Society.

Morrison, John G., Oakland. Died Nov 26, 1994, aged 80. Graduate of Rush Medical College, Chicago, Illinois, 1942. Licensed in California in 1947. Dr Morrison was a member of the Alameda-Contra Costa Medical Association.

Pigneri, Aldo G., Huntington Beach. Died Oct 19, 1994, aged 67. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Pigneri was a member of the Orange County Medical Association.

Prisinzano, Gandolfo A., Sacramento. Died October 25, 1994, aged 85. Graduate of Stanford University School of Medicine, Stanford, California, 1934. Licensed in California in 1934. Dr Prisinzano was a member of the Sacramento-El Dorado Medical Society.

Rodgers, David Leigh, San Francisco. Died Oct 26, 1994, aged 71. Graduate of University of Rochester School of Medicine and Dentistry, Rochester, New York, 1946. Licensed in California in 1951. Dr Rodgers was a member of the San Francisco Medical Society.

Rothe, Ronald E., Banning. Died Oct 13, 1994, aged 86. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1944. Licensed in California in 1944. Dr Rothe was a member of the Riverside County Medical Association.

Sachs, David D., San Francisco. Died Dec 8, 1994, aged 64. Graduate of Tufts University School of Medicine, Boston, Massachusetts, 1959. Licensed in California in 1960. Dr Sachs was a member of the San Francisco Medical Society.

Shipp, James F., Santa Barbara. Died Oct 28, 1994, aged 69. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1953. Licensed in California in 1956. Dr Shipp was a member of the Santa Barbara County Medical Society.

Siegel, Howard F., San Jose. Died Oct 5, 1994, aged 65. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Siegel was a member of the Santa Clara County Medical Association.

Tueller, Edward E., Burlingame. Died Dec 8, 1994, aged 72. Graduate of University of California, San Francisco, School of Medicine, 1948. Licensed in California in 1948. Dr Tueller was a member of the San Mateo County Medical Association.

Upham, A. Tyler, Orange. Died Oct 15, 1994, aged 49. Graduate of University of California, Los Angeles, School of Medicine, 1971. Licensed in California in 1972. Dr Upham was a member of the Orange County Medical Association.

Denver Medical Society

Owens, James Cuthbert. Died Dec 2, 1994, aged 78. Graduate of Marquette University, Milwaukee, Wisconsin, 1941. Licensed in Colorado in 1951.

New Mexico Medical Society

Bollinger, C. Colbert, Albuquerque. Died Apr 16, 1994, aged 63. Graduate of University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, 1957. Licensed in New Mexico in 1968. Dr Bollinger was a member of the Greater Albuquerque Medical Association.

(Continued from Page 14)

April 22-23—**Minimal Intervention in Vascular Disease.** Scripps Memorial Hospital and Scripps Clinic and Research Foundation at Hyatt Regency, San Diego. Sat-Sun. Contact: Laurel Steigerwald, Scripps Clinic. 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

February 5-7—**Ambulatory Obstetrics and Gynecology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Tues. 14.5 hrs. $300. Contact: UCD.

February 9-12—**50th Annual Postgraduate OB/GYN Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OGASC, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 18-24—**Perinatal Medicine.** USC at Westin Maui Hotel, Hawaii. Sat-Fri. 30 hrs. $595. Contact: USC.

ONCOLOGY

February 20-23—**Clinical Hematology and Oncology:** 1995. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 28 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 10-14—**20th Annual Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

February 17-18—**Comprehensive Cosmetic Blepharoplasty: Options and Finesse.** UCLA Jules Stein Institute. Fri-Sat. 16 hrs. $250. Contact: Angela O'Mara-Barnes, Meeting Coordinator, 359 San Miguel Dr, Ste 303, Newport Beach 92660. (714) 760-1522.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

ORTHOPEDICS

May 18-21—**10th Annual Symposium of the Spine Study Group.** Spine Study Group at Westin Mission Hills, Rancho Mirage. Thurs-Sun. Contact: Pat Curl, Meeting Coordinator, 4805 Mercury St, Ste E, San Diego 92111. (619) 279-9955.

OTOLARYNGOLOGY

February 5-10, February 26-March 3—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach.** UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

PATHOLOGY

February 15-18—**Review of Current Methods in Blood Banking and Transfusion Medicine.** American Society of Clinical Pathologists at Wyndham Hotel, Palm Springs. Wed-Sat. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612-3798. (800) 621-4142.

February 28-March 4—**Classical Morphologic Approaches and Newer Diagnostic Techniques to Blood Disorders.** American Society of Clinical Pathologists at Meridien Hotel in Coronado Island, San Diego. Tues-Sat. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612-3798. (800) 621-4142.

March 1-5—**34th Annual Convention and Scientific Exhibit Show of the Osteopathic Physicians and Surgeons of California.** American Osteopathic Society at Anaheim Hilton and Towers. Wed-Sun. 46 hrs. $495. Contact: Kimberley Bauer, OPSC, 455 Capitol Mall, Ste 230, Sacramento 95814. (916) 447-2004.

April 1—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 25-27—**Current Issues in Anatomic Pathology: 1995.** UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF

PEDIATRICS

February 4—**Update in Behavioral and Developmental Pediatrics.** UCSF at Millberry Union Conference Center, San Francisco. Sat. 6.5 hrs. $110. Contact: UCSF.

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 3-5—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

March 31-April 1—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center and UCSD at Hyatt Regency, La Jolla. Fri-Sat. 12.75 hrs. $245. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

May 4-6—**28th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

PSYCHIATRY AND NEUROLOGY

February 15-17—**Recent Advances in Neurology.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Fri. 15.5 hrs. $365. Contact: UCSF

February 23-26—**Breakthroughs in Psychiatry and the Law: Dangerousness and Its Discontents.** UCSD at La Jolla Marriott. Thurs-Sun. 15.5 hrs. $310. Contact: UCSD.

February 25-26—**You Will Learn Hypnosis: The Basic Skills.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $325. Contact: SCSCH, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

February 26—**Healing With Heart: Manifesting Magnificent Metaphors.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sun. 6 hrs. $180. Contact: SCSCH, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

March 31-April 2—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at La Jolla Marriott. Fri-Sun. 16 hrs. $525. Contact: UCSD.

April 7-9—**West Coast Neuropsychology Conference: New Advances in the Assessment and Treatment of Cognitive Deficit in School-Age Children.** UCSD at Pan Pacific Hotel, San Diego. 14.5 hrs. $325. Contact: UCSD.

July 25-30—**Neuropsychiatric Emergencies and Crisis Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea, Hapuna Beach Hotel, Hawaii. Tues-Sun. Contact: Ann McCormick, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102

PULMONARY MEDICINE

January 26-28—**Pulmonary Medicine and Surgery: New Approaches to Diagnosis and Treatment.** UCSD at Hotel del Coronado. Thurs-Sat. 18 hrs. $500. Contact: UCSD

January 28—**Rhinitis—Sinusitis and Atopic Dermatitis: Evaluation, Treatment, Mechanisms and Relevance to Asthma.** Huntington Memorial Hospital at Braun Auditorium, Pasadena. Sat. Vivian Mishalany, 39 Congress St, Ste 301, Pasadena 91105. (818) 397-3383.

(Continued on Page 83)

CONTINUING MEDICAL EDUCATION

(Continued from Page 82)

February 3-5—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Sheraton Desert Inn, Las Vegas, Nevada. Fri-Sun. 12 hrs. Contact: Karen DeBont, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528.

RADIOLOGY

March 5-9—**Neuro and Musculoskeletal MR.** UCSD at Hotel Del Coronado, San Diego. Sun-Thurs. 30 hrs. $600. Contact: Dawne Ryals, Ryals & Associates, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-10—**General Radiology Review.** UCLA at Guest Quarters Suite Hotel, Santa Monica. 40 hrs. $420. Contact: UCLA.

March 5-10—**Magnetic Resonance Imaging of the Brain, Spine and Musculoskeletal System.** UCSD at Hotel del Coronado. Sun-Fri. 30 hrs. $625. Contact: UCSD.

March 10-12—**Musculoskeletal Imaging**. UCSD at Hotel del Coronado. Fri-Sun. Contact: UCSD.

March 13-15—**15th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Mon-Wed. 18 hrs. $350. Contact: UCSF.

April 16-21—**15th Annual Residents' Radiology Review Course**. UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. 8 hrs. $135. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21-23—**Mammography Update and Review.** UCSD at Hotel Del Coronado, San Diego. Fri-Sun. 16 hrs. $350. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 84)

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1995 CME PROGRAMS

18th Annual Advanced Ultrasound Seminar: OB/GYN
February 2-4, 1995
Disney Yacht and Beach Club

16th Annual International Gastroenterology Conference
February 8-11, 1995
The Hilton, Walt Disney World Village

17th Annual Management of the Tiny Baby Conference
February 16-18, 1995
Disney Contemporary Hotel
(for more information call 407-841-5218)

6th Annual Emergency Medicine for the Critically Ill and Injured
February 23-26, 1995
Disney Grand Floridian Beach Resort

5th Annual Breast Imaging Conference
March 9-11, 1995
Yacht and Beach Club Resorts,
Walt Disney World Village

19th Annual Internal Medicine Series
March 27 - April 1, 1995
The Hilton, Walt Disney World Village

19th Annual Infectious Disease & Antibiotic Therapy Conference
March 22-25, 1995
The Hilton, Walt Disney World Village

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(Continued from Page 83)

SLEEP MEDICINE

January 28—**Sleep Medicine: Practices for the 21st Century.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

February 3-4—**Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. Contact: USC.

February 6-10—**18th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hyatt Islandia, San Diego. Mon-Fri. 26 hrs. $475. Contact: UCSD.

February 11-12—**Endoscopic Plastic Surgery and Beyond.** UCSD at BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD

March 24-25—**7th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 20-22—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, Nob Hill, San Francisco. Thurs-Sat. Contact: UCSF.

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

February 13-16—**Topics in Clinical Medicine: Evidence Based Care Conference.** Group Health Cooperative of Puget Sound at Royal Waikoloan, Kona, Hawaii. Mon-Thurs. 19 hrs. $450. Contact: Group Health Cooperative, CEB-1, 201 16th Ave E, Seattle, WA 98112. (206) 326-3441.

February 13-17—**Physician Heal Thyself.** UCSD at Sheraton Harbor Island, San Diego. Mon-Fri. Contact: UCSD.

February 16-19—**2nd International Congress on Vitamins and Biofactors in Life Science.** Thurs-Sun. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 18-21—**Molecular Approaches to Laboratory Diagnosis.** UCSF at Ritz-Carlton, San Francisco. Sat-Tues. Contact: UCSF.

March 9-10—**Focus on Fungal Infections 5**. International Medical Experience Exchange at Sheraton Palace, San Francisco. Thurs-Fri. 14 hrs. Contact: Anita Reeves, IMEDEX USA, 1060 Cambridge Square, Ste D, Alpharetta, GA 30201. (404) 751-7332.

April 28—**The Cutting Edge 1995: How to Treat Difficult Patient.** UCSD at Pan Pacific Hotel, San Diego. Fri. 13 hrs. $325. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 28-February 2—**24th Annual Mid-Winter Conference of Colorado Ophthalmological Society.** Sheraton Steamboat, Steamboat Springs. Sun-Thurs. Contact: David R. Scott, (800) 394-4968.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

March 5-10—15th **Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center, (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

March 12-15—**5th International Conference on Pulmonary Rehabilitation and Home Ventilation**. National Jewish Center for Immunology and Respiratory Medicine and American Association for Respiratory Care at Hyatt Regency, Denver. Sun-Wed. Contact: Adele Gelfand, (303) 398-1359 or 270-2171.

July 28-August 1—**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 17-19—**Ada County Medical Society—36th Annual Medical Winter Clinics—From Trauma to Rehab.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, members; $175, nonmembers. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930 or Marie Chester, (208) 386-2135.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting.** Hilton Hotel of Santa Fe. Sat. Contact: Lynette Hanks, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 84)

July 3-7—**Santa Fe Breast Imaging.** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging**. Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Eldorado Hotel, Santa Fe. Contact: Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 6-10—**Surgical Pathology.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $550. Contact: UUSM.

February 13-17—**Update in Clinical Microbiology and Immunology**. University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 13-17—**Brigham-Utah Therapeutic GI Endoscopy Course 1995: Problems, Decisions, Techniques**. University of Utah School of Medicine at the Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 15-18—**Physical Medicine and Rehabilitation Update**. University of Utah School of Medicine at Olympia Park Hotel, Park City. Wed-Sat. Contact: UUSM.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 23-March 2—**40th Annual Postgraduate Course in Anesthesiology—Pediatric and Obstetrical Anesthesia: 1995 Update.** University of Utah School of Medicine at Snowbird Cliff Lodge. One week. Contact: UUSM.

February 26-March 1—**36th Annual OB/GYN Update**. University of Utah School of Medicine at the Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 1-4—**OB/GYN Update in Endocrinology and Infertility**. University of Utah School of Medicine at the Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-10—**Advances in Internal Medicine.** University of Utah School of Medicine at Cottonwood Center, Snowbird. Mon-Fri. Contact: UUSM.

March 10—**Ophthalmology—Resident/Alumni Day**. University of Utah School of Medicine. Fri. Contact: UUSM.

(Continued on Page 86)

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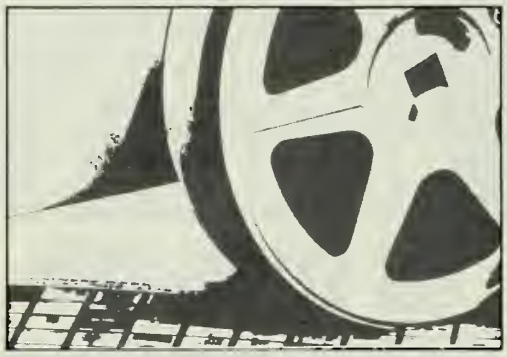

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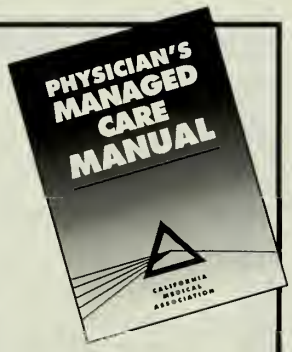

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Price: $50 CMA members, $100 non-members.

(Continued from Page 85)

March 10-11—**Western Intermountain Neurological Organization**. University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

June 7-10—1995 **Summer Pediatric Neurosurgery Symposium**. University of Utah School of Medicine at Stein Eriksen Lodge in Deer Valley, Park City. Wed-Sat. Contact: UUSM.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

(Continued on Page 87)

CONTINUING MEDICAL EDUCATION

(Continued from Page 86)

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 26—**Cancer Care Symposium**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

January 26—**Dilemmas in Breast Cancer**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

January 26-27—**A Day in the Office: Problems in Pediatric Practice**. Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

January 27-28—**ACLS**. Harrison Memorial Hospital, Bremerton. Fri-Sat. Contact: Harrison Hospital, (206) 792-6765.

February 1-5—**CME at Whistler.** Tacoma. Wed-Sun. Contact: College of Medical Education, (206) 627-7137.

February 3—**Depression Symposium**. Seattle. Fri. Contact: Providence, (206) 320-2552.

February 18—**Asthma Symposium**. Seattle. Sat. Contact: Access Com., (708) 550-0090.

February 24-25—**Transplantation Issues, Needs and Opportunities in the African-American Community**. Seattle. Fri-Sat. Contact: Providence, (206) 320-2552.

March 2—**Diagnosis and Treatment of Insomnia in Clinical Practice**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 5-10—**17th Annual Winter Psychiatry Conference: Coping With Current Issues in Clinical Practice**. Park City, Utah. Sun-Fri. Contact: Menninger Continuing Education, (800) 288-7377.

March 6-8—**The Best Approach: Effective, Efficient Strategies in Clinical Practice and Prevention.** Seattle. Mon-Wed. Contact: Group Health, (206) 326-3441.

March 9—**Family Practice Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 16—**Radiation Safety, Challenge, Change, and Compliance.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

May 5-6—**Mental Health Update.** U/W. Fri-Sat. Contact: U/W.

June 1-3—**Primary Care Update of OB-GYNs.** Seattle. Thurs-Sat. Contact: U/W.

June 2-3—**6th Update on Travel and International Medicine**. Seattle. Fri-Sat. Contact: U/W.

June 7-10—**Bariatric Medicine**. Seattle. Wed-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762. ◆

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ISSN #0093-0415 PUBLISHED SINCE 1904 TAX ID 94-0359340

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

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Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 27-30, 1995, Resort at Squaw Creek, 1995.

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Center For Musculoskeletal Tumors

Malignant tumors of the musculoskeletal system, whether bone or soft tissue tumors, are extremely rare: only an estimated 4,000 new cases of osteogenic sarcoma, and 6,000 new cases of soft tissue sarcomas of the extremities, are diagnosed each year. Consequently, orthopaedic surgeons in private practice may see a malignant bone tumor perhaps once every 10 years.

A CASE STUDY

A 35-year-old law student developed pr gressive pain in his hip. He eventua fell, sustaining a fracture through femoral neck. At that time, a big tum was detected in the proximal third of t femur, with the added complication spillage into the hip joint. A biopsy co firmed an osteosarcoma, with no e dence of metastatic tumor. After thr courses of chemotherapy, the patie underwent surgery.

This was a complicated case becau of the tumor spillage. In order to achie an adequate margin around the tum Dr. Menendez not only had to remove t proximal femur and surrounding musc lature, but also the entire hip joint bloc, including acetabulum, as we Because the patient asked the team reconstruct a leg that he could walk and a hip he could move, surgeons opt against a fusion and instead performed procedure that involved an allograft reconstruct the acetabulum, and a custo endoprosthesis to replace the joint.

Following surgery, the patient unde went some follow-up chemotherapy. had essentially 100 percent tumor necr sis, and an excellent response to chem therapy. His allografts and junctions ha since healed, and after a year he is amb lating with a cane — and continuing pursuit of a law degree.

In sharp contrast, Lawrence R. Menendez, M.D., associate professor of Orthopaedic Surgery at the University of Souther California School of Medicine and director of Orthopaedic Oncology at USC University Hospital, performs more than 20 procedures a year. This volume, supported by a multidisciplin team of medical oncologists, musculoskeletal pathologists, vas lar and plastic surgeons and radiation therapists, along with nursing, social and rehabilitative services at USC University H pital, has allowed Dr. Menendez to develop and maintain an expertise in this specialized field.

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Bone Tumors

Benign and malignant bone tumors each present its own specific treatment challenges, making it imperative that an accurate diagnosis be established. Dr. Menendez treats the most common malignant bone tumor, osteogenic sarcoma, with biopsy and then he develops a comprehensive treatment strategy that may include staging studies, pre- and post-operative treatment with chemotherapy and/or radiation therapy, surgery and reconstruction, rehabilitation, and long-term follow-up to detect tumor recurrence. Reconstruction options include allografts, autologous bone grafts, prosthetic implants or a combination of these materials.

Soft Tissue Tumors

Soft tissue tumors that appear benign may actually be malignant, again requiring absolute accuracy of diagnosis. Oftentimes, large soft tissue resections will require extensive reconstructive surgery involving vascularized flaps to provide tissue coverage. At USC, Dr. Menendez has immediate access to the expertise of vascular surgeons, general surgeons and reconstructive surgeons to provide necessary treatment. As a result, he is prepared for any situation.

Close Contact With Referring Physicians

Follow-up is a vital aspect of the program. Dr. Menendez examines X-rays and exchanges notes with referring physicians, keeping all parties involved. He sends referring physicians a letter every time he sees their patients in follow-up, whether it is a month or five years later. Dr. Menendez follows patients who had malignancies every three months for the first two years, and then every six months. Regular check-ups are recommended for the life of the patient, although Dr. Menendez considers the patient cured if five years pass without a recurrence of metastatic disease.

Lawrence R. Menendez, M.D.:
At the forefront of orthopaedic oncology

About the Director

Lawrence R. Menendez, M.D., predicts that the future of musculoskeletal oncology will be centered within the major academic centers across the country, and believes USC is well-positioned to offer leadership in this complex field.

Born and raised in New Jersey, Dr. Menendez attended Middlebury College in Vermont, where he received his bachelor's degree in biology. He earned his medical degree from the New York University School of Medicine, completed a general surgery internship at Columbia Presbyterian Medical Center, and returned to New York University for his orthopaedic surgery residency. He also did an oncology fellowship at the University of Florida with William F. Enneking, M.D., one of the founders of orthopaedic oncology as a specialty.

From 1985 to 1989, Dr. Menendez served on the full-time USC faculty as assistant professor of Orthopaedic Surgery, and then became a part-time faculty member, moving his private practice to The Hospital of the Good Samaritan in Los Angeles. During this time, he continued to run the orthopaedic oncology service at Los Angeles County+USC Medical Center. In July 1992, he was recruited back to USC full time as associate professor.

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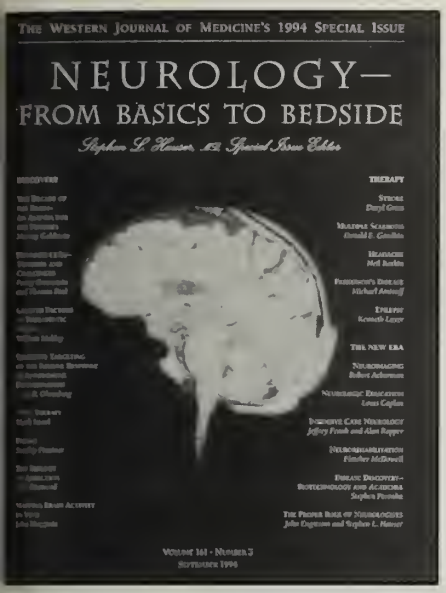

Stephen Hauser, MD
Special Issue Editor, 1994

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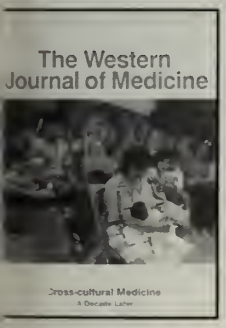

Judith Barker, PhD
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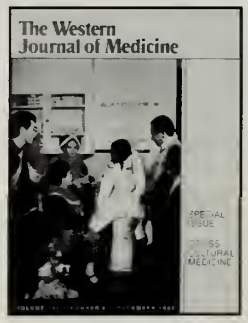

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We prospectively assessed the safety and efficacy of laparoscopic jejunostomy done by 11 surgeons in 8 medical centers using the T-fastener technique. In all, 23 men and 13 women aged 19 to 84 (mean, 59) years required enteral feeding, but could not undergo gastrostomy and had no contraindication to laparoscopy. Of these patients, 12 had head and neck cancer and 11 had neurologic swallowing dysfunction. The procedure took 25 to 180 minutes (mean, 75). Three (8%) early cases were converted to open jejunostomy because of accidental enterotomies caused by inappropriate techniques that were avoided in later cases. Minor technical problems, such as passing a needle through the back wall of the jejunum, occurred in 7 patients, but they were easily corrected and produced no complications. Feedings were routinely begun within 24 hours of the surgical procedure. All jejunostomy catheters functioned well. This is a safe and effective technique when done by experienced laparoscopic surgeons, and serious complications are rare.

LAPAROSCOPIC JEJUNOSTOMY
ENTERAL FEEDING
LAPAROSCOPY
LAPAROSCOPIC SURGERY

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(triamcinolone acetonide)

Please see brief summary of prescribing information on following page.

1 ONCE DAILY Nasacort® Nasal Inhaler

(triamcinolone acetonide)

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Shake Well Before Using
BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m²/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m²/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m²/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m²/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m²/day or 110 mcg/m²/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m²/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m²/day and 7.0 mcg/m²/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m²/day in the rat and 320, 640 and 1280 mcg/m²/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m²/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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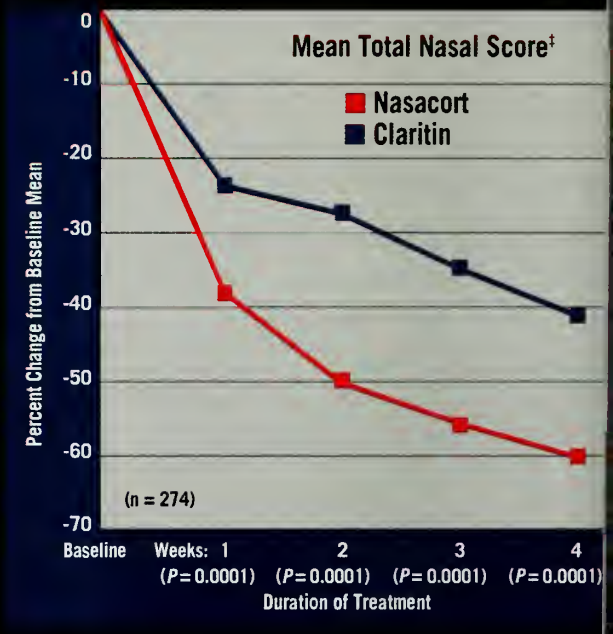
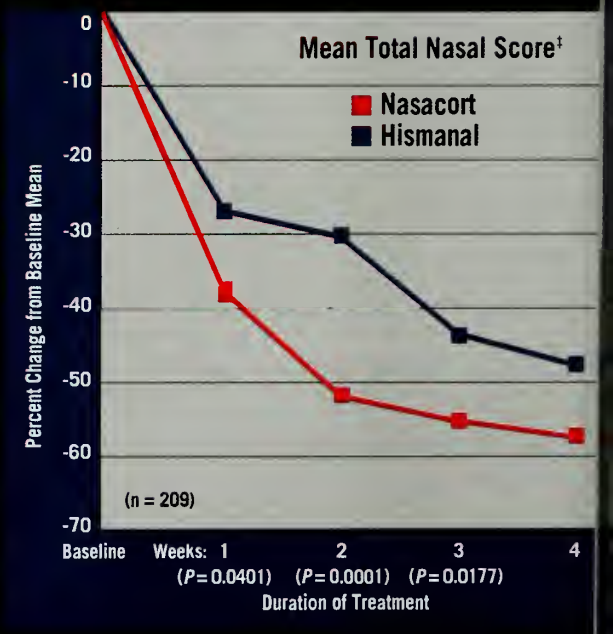
Superior symptomatic relief vs. QD non-sedating antihistamines[1]

NASACORT VS. CLARITIN[1,2]*



‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[1,3]*



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*

† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*

§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

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1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

ABSTRACTS FEBRUARY 1995

(Komaromy M, Lurie N, Bindman AB: California physicians' willingness to care for the poor. West J Med 1995; 162:127-132)

Although generalist physicians appear to be more likely than specialists to provide care for poor adult patients, they may still perceive financial and nonfinancial barriers to caring for these patients. We studied generalist physicians' attitudes toward caring for poor patients using focus groups and used the results to design a survey that tested the generalizability of the focus group findings. The focus groups included a total of 24 physicians in 4 California communities; the survey was administered to a random sample of 177 California general internists, family physicians, and general practitioners. The response rate was 70%. Of respondents, 77% accepted new patients with private insurance; 31% accepted new Medicaid patients, and 43% accepted new uninsured patients. Nonwhite physicians were more likely to care for uninsured and Medicaid patients than were white physicians. In addition to reimbursement, nonfinancial factors played an important role in physicians' decisions not to care for Medicaid or uninsured patients. The perception of an increased risk of being sued was cited by 57% of physicians as important in the decision not to care for Medicaid patients and by 49% for uninsured patients. Patient characteristics such as psychosocial problems, being ungrateful for care, and noncompliance were also important. Poor reimbursement was cited by 88% of physicians as an important reason not to care for Medicaid patients and by 77% for uninsured patients. Policy changes such as universal health insurance coverage and increasing the supply of generalist physicians may not adequately improve access to care unless accompanied by changes that address generalist physicians' financial and nonfinancial concerns about providing care for poor patients.

MEDICAID PATIENTS REIMBURSEMENT
UNINSURED PATIENTS

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 16-18—**Mayo Interactive Surgical Symposium**. Mayo Clinic-Scottsdale at the Orange Tree Golf and Conference Resort, Scottsdale. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 16-18—**18th Annual Midwinter Symposium—Advances in Obstetrics and Gynecology**. Maricopa Medical Center and Phoenix Ob/Gyn Society at Scottsdale Plaza Resort. Thurs-Sat. Contact: Beverlee Anderson, (602) 267-5366.

February 17-20—**21st Annual Scientific Meeting—Anesthesia for the 90s**. University of Arizona College of Medicine and Arizona Society of Anesthesiologists at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sun. Contact: (602) 947-5400.

February 20-23—**Practical Radiology.** University of Arizona College of Medicine at Loews Ventana Canyon Resort, Tucson. Mon-Thurs. Contact: Lynne Mascarella, U of A.

February 23-24—**Hepatology Update 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Thurs-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 23-25—**21st Annual Frontiers in Ophthalmology.** St Luke's Medical Center at Red Lion's La Posada Resort, Scottsdale. Thurs-Sat. Contact: (602) 274-7479.

February 24-25—**Benjamin Burrows Desert Lung Conference.** University of Arizona College of Medicine at the Rio Rico Resort, Rio Rico. Fri-Sat. Contact: U of A.

February 24-25—**Mayo Plastic Surgery Symposium.** Mayo Clinic-Scottsdale at the Ritz-Carlton Hotel, Phoenix. Fri-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

February 24-26—**1995 Scientific Assembly—American Academy of Family Practice.** The Pointe Hilton at Tapatio Cliffs, Phoenix. Fri-Sun. Contact: American Academy of Family Practice, Arizona Chapter, (602) 249-2021.

February 27-March 2—**Pediatric Update.** Phoenix Children's Hospital at Marriott's Camelback Inn, Scottsdale. Mon-Thurs. Contact: (602) 239-5783.

March 5-9—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at Marriott's Camelback Inn Resort, Scottsdale. Sun-Thurs. Contact: Lynne Mascarella, U of A.

March 8-10—**Clinical Reviews 1995.** Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Wed-Fri. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Frequently Encountered GYN Problems in Primary Care**. Mayo Clinic-Scottsdale at the Ritz-Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 11—**Controversies in Hypertension.** Mayo Clinic-Scottsdale at the Ritz Carlton, Phoenix. Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 16-18—**22nd Annual Symposium—Recent Advances in Neurology and Neurosurgery**. University of Arizona and Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Thurs-Sat. Contact: Beverly Pennington, (602) 406-3067.

March 17-19—19th **Annual James H. McDonald Urological Seminar.** Maricopa Medical Center and Phoenix Urologic Society at Scottsdale Plaza Resort. Fri-Sun. Contact: Beverlee Anderson, (602) 267-5366.

March 25-30—**Skeletal Radiology.** Allegheny General Hospital and Medical College of Pennsylvania at the Arizona Biltmore, Phoenix. Sat-Thurs. Contact: (412) 359-4952.

March 30-April 1—**4th Annual Urogynecology and Disorders of the Pelvic Floor**. Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30-April 2—**Mammography in March: Breast Diseases and Imaging**. Maricopa Medical Center at Marriott Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

April 2-7—**Management Development for Department Chairs Programs A and B**. American College of Physicians Executives at the Wyndham Paradise Valley Resort, Scottsdale. Sat-Fri. Contact: (800) 562-8088.

April 4-7—**Current Issues in Primary Care Medicine**. Pacific Northwest Medical Education Institute, Inc, at the Pointe Hilton at Squaw Peak, Phoenix. Tues-Fri. Contact: (206) 261-2160.

April 4-8—**1995 Annual Meeting—Arizona Osteopathic Medical Association**. Wyndham Paradise Valley Resort, Scottsdale. Tues-Sat. Contact: (602) 840-0460.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

April 6-8—**Lower Extremity Arthroplasty**. Mayo Foundation, Scottsdale. Thurs-Sat. Contact: (800) 323-2688.

April 6-9—**2nd Mayo Telemedicine Symposium and 2nd International Symposium on the Medical Aspects of Telemedicine**. Mayo Foundation. Sat-Tues. Contact: (800) 323-2688.

April 7-11—**1995 Annual Meeting**—South Central Association of Blood Banks. The Pointe at South Mountain, Phoenix. Fri-Tues. Contact: (512) 459-6600.

April 9-12—**Management Strategies in Complex Congenital Heart Disease**. Mayo Foundation, Scottsdale. Sun-Wed. Contact:: (800) 323-2688.

April 10-14—**Physician in Management Seminar III**. American College of Physician Executives at the Wyndham Paradise Valley Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

April 19-23—**Women's Health**. American Academy of Family Physicians at The Buttes, Tempe. Wed-Sun. Contact: (800) 926-6890, ext 5245.

April 20-22—**5th Annual Advances and Controversies in Clinical Nutrition**. Mayo Clinic/Mayo Foundation, Phoenix. Thurs-Sat. Contact: (800) 462-9633.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

June 23-25—**18th Annual Pediatrics in the Red Rocks**. American Academy of Pediatrics, Arizona Chapter, and Maricopa Medical Center at Los Abrigados Resort, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

(Continued on Page 114)

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FEBRUARY, 1995

The 2nd Annual Symposium on the Neurologist and Backpain
February 18-20, 1995
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16th Annual Symposium—Current Topics in Obstetrics
February 18-25, 1995
THE GANT CONDOMINIUMS
ASPEN, COLORADO

MARCH, 1995

Gynecologic Oncology for the Primary Care Physician
March 19-24, 1995
THE WESTIN RESORT
MAUI, HAWAII

Medical Disaster Response Training Course
March 30-31, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

APRIL, 1995

Advanced Urogynecology and Pelvic Surgery
April 5-9, 1995
MARQUIS HOTEL AND VILLAS
PALM SPRINGS, CALIFORNIA

4th Annual OB/GYN Ultrasound—The State of the Art
April 11-14, 1995
WESTIN RESORT
MAUI, HAWAII

20th Annual Care of the Sick Newborn Symposium
April 26-28, 1995
HYATT REGENCY HOTEL
LONG BEACH, CALIFORNIA

MAY, 1995

6th Annual Philip J. DiSaia Society—OB/GYN Symposium
May 19, 1995
DOUBLETREE HOTEL
ORANGE, CALIFORNIA

JUNE, 1995

UCI Family Practice Refresher Course
June 12-17, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

JULY, 1995

4th Annual Internal Medicine Board Review Course
July 31-August 4, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

AUGUST, 1995

13th Annual Controversies in Obstetrics and Gynecology
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Topic	Date	Location
Primary Care Medicine	February 19-24	Squaw Valley, California
Diabetes Update, Advances in Endocrinology & Metabolism	March 17-18	Ritz-Carlton, San Francisco
Emergency Medicine The Next 100 Years Paramedic Centennial Program	March 23-24	Holiday Inn, Financial District San Francisco
Primary Care Cardiology	April 1	ANA Hotel, San Francisco
Advances in Emergency Medicine	April 5-8	Ritz-Carlton, San Francisco
Primary Care Update	April 16-21	Inter-Continental Hotel, Maui, Hawaii
Advances in Infectious Diseases	April 26-28	Fairmont Hotel, San Francisco
Advances in Internal Medicine	May 22-26	Ritz-Carlton, San Francisco
Advances in Internal Medicine	June 19-23	UCSF Campus, San Francisco
Critical Care Cardiology	August 10-12	Ritz-Carlton, San Francisco
Essentials of Primary Care	August 20-25	Squaw Valley, California
Clinical Care of the AIDS Patient	August 24-29	Sun Valley, Idaho

CONTINUING MEDICAL EDUCATION

(Continued from Page 112)

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 18-21—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $350. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691

May 21-26—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 37.5 hrs. $500. Contact: UCSD.

CARDIOLOGY

March 2-4—**Use of 2-D Echocardiography and Echo Doppler in the Perioperative Period.** Thurs-Sat. 12 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 181)

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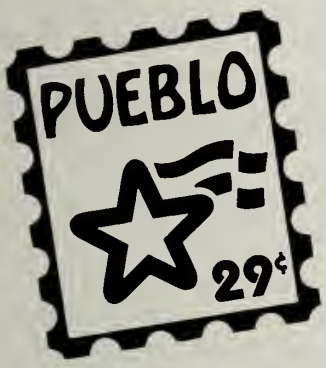

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
Lower Respiratory Tract Infections caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus, E. coli,* and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase producing strains of *E. coli, Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS–*Liver*).
Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Augmentin should not be co-administered with Antabuse® (disulfiram).
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS). A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
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* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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SmithKline Beecham Pharmaceuticals

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Articles

Prospective Evaluation of the Safety and Efficacy of Laparoscopic Jejunostomy

QUAN-YANG DUH, MD, *San Francisco, California*; ANDREA L. SENOKOZLIEFF-ENGLEHART, RN, MS, *Columbus, Ohio;* ALLAN E. SIPERSTEIN, MD, *and* JEFFREY PEARL, MD, *San Francisco, California;* JOHN P. GRANT, MD, *Durham, North Carolina*; PATRICK L. TWOMEY, MD, *San Francisco, California;* THOMAS R. GADACZ, MD, *Augusta, Georgia;* RICHARD A. PRINZ, MD, *Maywood, Illinois;* BRUCE M. WOLFE, MD, *Sacramento, California;* NATHANIEL J. SOPER, MD, *St Louis, Missouri;* ROBERT G. MARTINDALE, MD, *Fort Gordon, Georgia*; MARK McCAMISH, PhD, MD, *and* JEFFREY R. ROSS, MD, *Columbus, Ohio; and* LAWRENCE W. WAY, MD, *San Francisco, California*

We prospectively assessed the safety and efficacy of laparoscopic jejunostomy done by 11 surgeons in 8 medical centers using the T-fastener technique. In all, 23 men and 13 women aged 19 to 84 (mean, 59) years required enteral feeding, but could not undergo gastrostomy and had no contraindication to laparoscopy. Of these patients, 12 had head and neck cancer and 11 had neurologic swallowing dysfunction. The procedure took 25 to 180 minutes (mean, 75). Three (8%) early cases were converted to open jejunostomy because of accidental enterotomies caused by inappropriate techniques that were avoided in later cases. Minor technical problems, such as passing a needle through the back wall of the jejunum, occurred in 7 patients, but they were easily corrected and produced no complications. Feedings were routinely begun within 24 hours of the surgical procedure. All jejunostomy catheters functioned well. This is a safe and effective technique when done by experienced laparoscopic surgeons, and serious complications are rare.

(Duh QY, Senokozlieff-Englehart AL, Siperstein AE, et al: Prospective evaluation of the safety and efficacy of laparoscopic jejunostomy. West J Med 1995; 162:117-122)

Jejunostomy is indicated in patients who have a functioning gut, but are unable to eat and in whom gastrostomy is contraindicated or not possible. We developed a new technique for the percutaneous placement of a jejunostomy catheter, guided by laparoscopy (laparoscopic jejunostomy), in which T-fasteners are used to retract and anchor the jejunum. Preliminary experience showed it to be safe and simple to perform.[1] We report the results of a prospective, multicenter study using this laparoscopic jejunostomy technique.

Patients and Method

In all, 36 patients were enrolled prospectively over a six-month period from eight medical centers in the United States. Patients were included in the study if they had a functioning gut and required long-term enteral feeding because of existing or possible malnutrition and were not candidates for percutaneous endoscopic gastrostomy or laparoscopic gastrostomy or were undergoing other laparoscopic procedures. In these patients, jejunostomies rather than gastrostomies were indicated usually because of gastric abnormalities, such as gastroesophageal reflux and aspiration, gastroparesis, gastric outlet obstruction, or previous gastric resection.

Patients were excluded from the study if they had a contraindication for laparoscopy or jejunostomy, including nonfunctioning gut, pregnancy, morbid obesity, peritonitis, inflammatory bowel disease, massive ascites, a severe bleeding disorder, and severe adhesions from previous abdominal operations. The study protocol was reviewed and approved by the human research committee

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Dr Duh and Dr Way developed the procedure for creating laparoscopic enterostomy using the T-fastener technique. The Regents of the University of California hold the patent to this technique (US Patent No. 5,151,086). The Regents of the University of California have licensed Abbott Laboratories to use this patent for laparoscopic enterostomy kits. Dr Duh and Dr Way may be entitled to a share of the royalties. Drs McCamish and Ross and Ms Senokozlieff-Englehart are employees of Abbott Laboratories.

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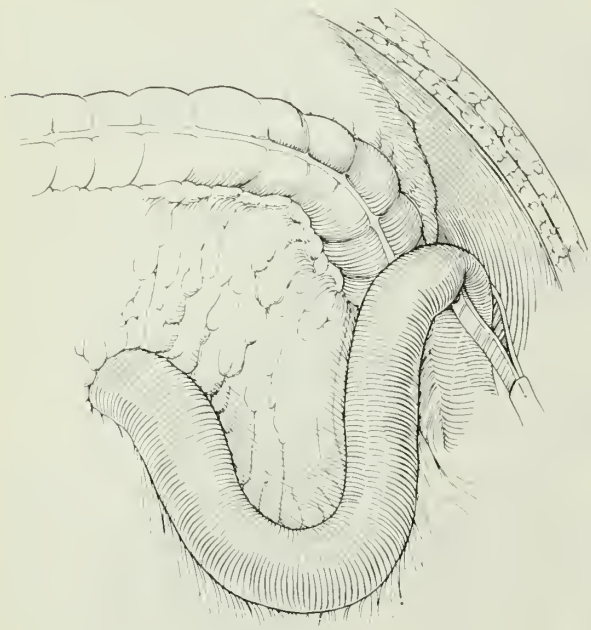

Figure 1.—The proximal jejunum and the ligament of Treitz are identified by lifting the transverse mesocolon and running the small bowel with the graspers.

of each medical center, and informed consent was obtained from each patient. One case was done with the patient under intravenous sedation; all the others were done with the patients under general anesthesia. Video recordings of the procedures were reviewed by one of the authors (Q.-Y. D.). The patients were examined by the operating surgeon after the procedure and were observed for at least two weeks. Causes for complications and conversions were analyzed after the first 25 cases and used to improve the results for the subsequent cases. The procedure was performed as previously described (Figures 1 through 5).[1]

Results

There were 23 men and 13 women, ages 19 to 84 years (mean, 59 years). Of these, 12 patients (33%) had head and neck cancer, 11 (31%) had neurologic deficit, and 13 (36%) had esophageal cancer and other diseases requiring jejunostomy for treatment or prevention of malnutrition. In all, 9 patients (25%) had had previous abdominal operations. Serum levels of albumin were 13 to 48 grams per liter, with a mean of 31 grams per liter (1.3 to 4.8 grams per dl, with a mean of 3.1 grams per dl). The procedures lasted 25 to 180 minutes (mean, 75 minutes). Of these, 4 were done with a concurrent laparoscopic gastrostomy.

TABLE 1.—*Conversion, Complications, and Death in 36 Patients Who Underwent Laparoscopic Jejunostomy*

Result	Patients No.	Patients %
Converted to open jejunostomy*	3	8
Postoperative complications	4	11
Volvulus required laparotomy	1	
Wound erythema or infection†	3	
Catheter dislodged postoperatively‡	5	14
Death (<30 days postoperatively)§	4	11

*One jejunal injury was caused by a grasper, two by the catheter.
†One patient required antibiotics.
‡All were replaced, two by repeat laparoscopy.
§All died of underlying diseases; the jejunostomies all functioned well.

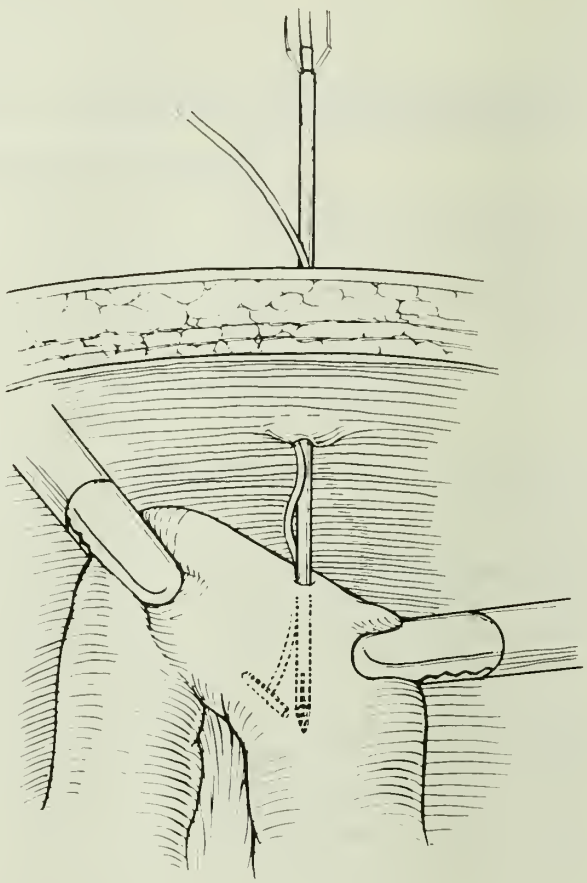

Figure 2.—The T-fastener is introduced percutaneously and discharged into the lumen from the slotted needle by the stylet. Note the oblique angle of the needle to the jejunum to avoid perforation through the back wall or into the mesentery.

Operative

Three cases (8%) were converted to open jejunostomy because of accidental enterotomies, one by graspers and two by the catheter (Table 1). Another patient, who had a successful laparoscopic jejunostomy, had laparotomy because of a failed concomitant gastrostomy. Other minor intraoperative problems were easily corrected without complications and did not require laparotomy. The slotted needle penetrated the back wall of the jejunum in two patients; the needle holes did not require suturing. One T-fastener had to be cut and replaced to achieve optimal placement in five patients.

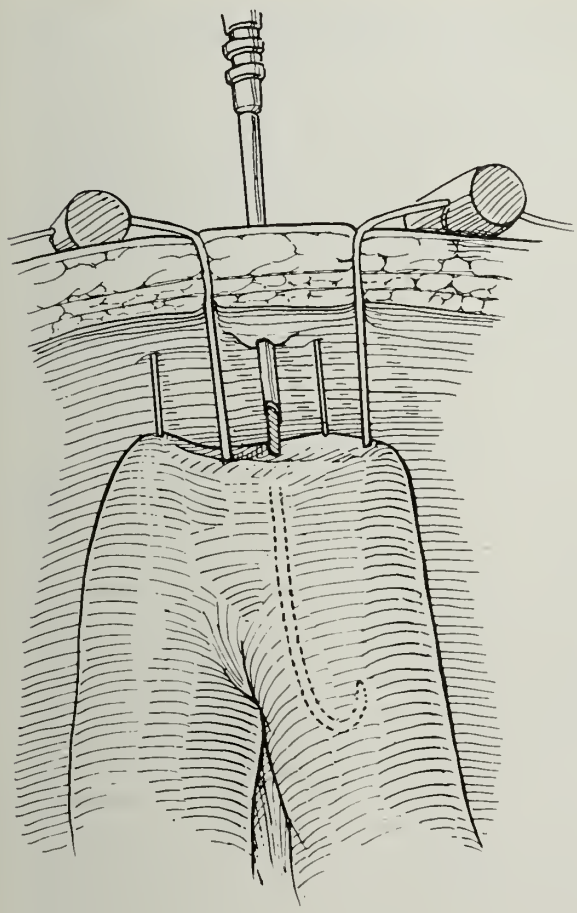

Figure 3.—Four T-fasteners are used to retract the antimesenteric jejunal wall. A J-wire is introduced into the lumen of the jejunum through an 18-gauge needle.

Postoperative

In one patient (3%), a 34-year-old woman, a volvulus developed around the jejunostomy site, requiring laparotomy one day after the procedure. In three patients (8%), local erythema developed, in two at a T-fastener site, and in one at the jejunostomy site. They were treated by removing the T-fasteners; one patient received antibiotics. Five patients (14%) required the replacement of catheters when they were removed accidentally. One was replaced in the emergency department, and one was replaced on the ward. One was replaced twice, once in the emergency department and once under fluoroscopy. Two were replaced by repeat laparoscopy (see Table 1). The jejunostomy catheters all functioned well. Episodes of clogging were few and were easily treated by flushing the catheters with saline solution.

In our study, 4 patients (11%) died within 30 days of the procedure (Table 1). A 76-year-old man with a thoracic epidural abscess died of respiratory failure 8 days after the procedure. A 74-year-old man, who had severe peripheral vascular disease and failure to thrive, died 13 days after a jejunostomy of sepsis originating from his below-the-knee amputation site. A 79-year-old man, who had an emergent aortic valve replacement, died of multisystem failure 7 days after the jejunostomy. A 46-year-old man with squamous cell carcinoma of the floor of the mouth died of disseminated cancer 15 days later at home. All of them had a functioning, nonleaking jejunostomy. Autopsies on the first two patients showed the jejunostomy to be intact.

Discussion

We recently developed a laparoscopic technique for placing catheters inside the bowel by anchoring them with T-fasteners.[2] We have applied this laparoscopic

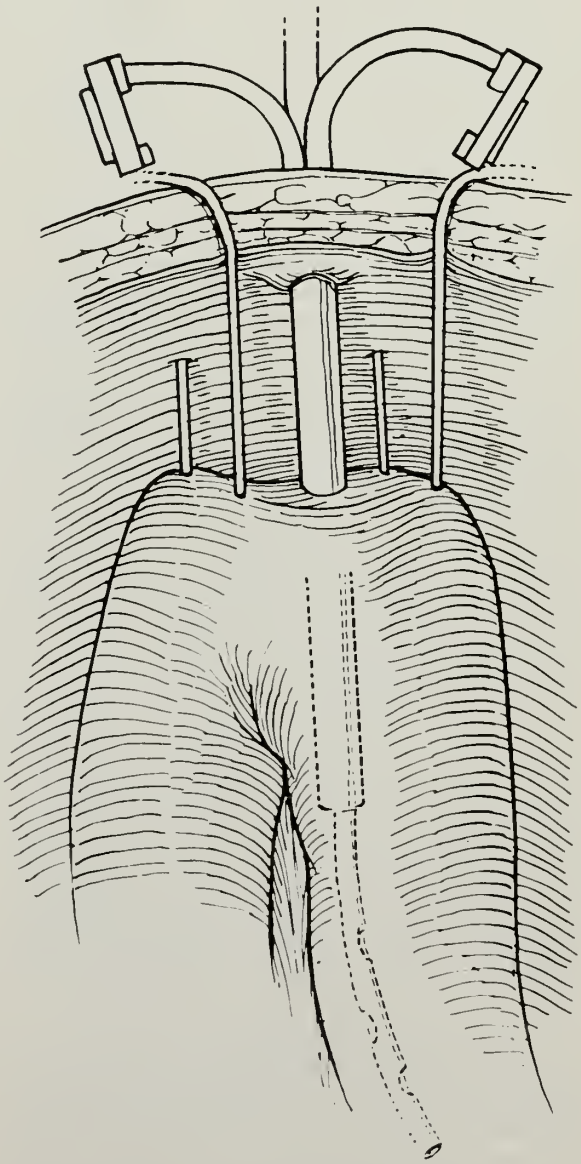

Figure 4.—The jejunostomy catheter is placed through the peel-away introducer, which is then removed.

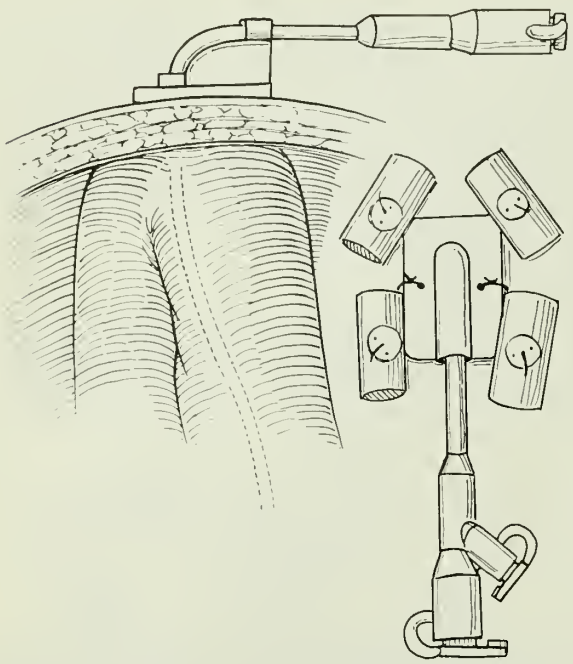

Figure 5.—The T-fasteners and the jejunostomy catheter are secured to the abdominal wall. The T-fastener sutures are cut 2 weeks later, and the metal T-bars are allowed to pass in the stool.

technique successfully to place gastrostomies,[3] jejunostomies,[1] and cecostomies.[4] This multicenter prospective study was designed to evaluate the safety and efficacy of this technique for laparoscopic jejunostomy in a large group of patients.

Three of the patients (8%) required laparotomy because of accidental enterotomies. These occurred early in the study and were the result of inappropriate techniques. One was caused by traumatic retraction on the bowel by graspers that were not designed to hold the bowel. One was caused by the forceful introduction of the catheter at a 90-degree angle through an introducer, the tip of which was against the back wall of the jejunum. One occurred in a patient with poor tissue who was receiving steroids and chemotherapy. The first two enterotomies were small and could have been closed by laparoscopic suturing without laparotomies; laparotomies were done because of our protocol requirement. Neither abdominal or wound infection developed in any of the three patients. The rate of conversion to open jejunostomy is expected to be negligible once a surgeon gains experience in manipulating the small bowel.

Because laparoscopic manipulation of the bowel requires some practice, only surgeons with advanced laparoscopic training should do laparoscopic jejunostomy. Because laparoscopic gastrostomies are easier to do than laparoscopic jejunostomies, we recommend that the surgeons gain experience first with laparoscopic gastrostomies before attempting laparoscopic jejunostomies.

Minor technical problems, such as placing the needles through the back wall of the jejunum, also occurred in early cases and became rare with the increasing experience of the surgeons. T-fasteners can be most accurately placed if the jejunum is well distended by insufflating air through a nasogastric or orogastric tube or through the slotted needle when the first T-fastener is introduced. A misplaced T-fastener can be removed or, if it is already inside the lumen of the bowel, cut and allowed to pass with the stool. The alignment of the T-fasteners in a "diamond" pattern on the jejunum and the abdominal wall is crucial. Tension exerted by the T-fasteners because of misalignment can tear the jejunum.

The procedure time decreased as the surgeons gained experience (Figure 6). An uncomplicated laparoscopic jejunostomy should take 30 to 45 minutes. This is no more than the time it usually takes for an open jejunostomy. Laparoscopic jejunostomies have been done using only local anesthesia, although with more difficulty because the pneumoperitoneum is limited. A kit for laparoscopic jejunostomy (Flexi-Flo Lap J Kit; Ross Product Division, Abbott Laboratories, Columbus, Ohio) has been approved by the Food and Drug Administration and is priced similar to other kits for percutaneous endoscopic gastrostomies and laparoscopic gastrostomies. The cost of laparoscopic jejunostomy, therefore, may not differ substantially from that of open jejunostomy.

Volvulus around the jejunostomy site is a serious complication. It occurred in one of our patients and was corrected by laparotomy. Volvulus can also occur in patients with open jejunostomy.[5] It is most likely caused by the small area of bowel that is fixed to the anterior abdominal wall and the mobility of the small bowel. The diamond-shaped alignment of the T-fasteners, affixing a longer portion of the jejunum to the anterior abdominal

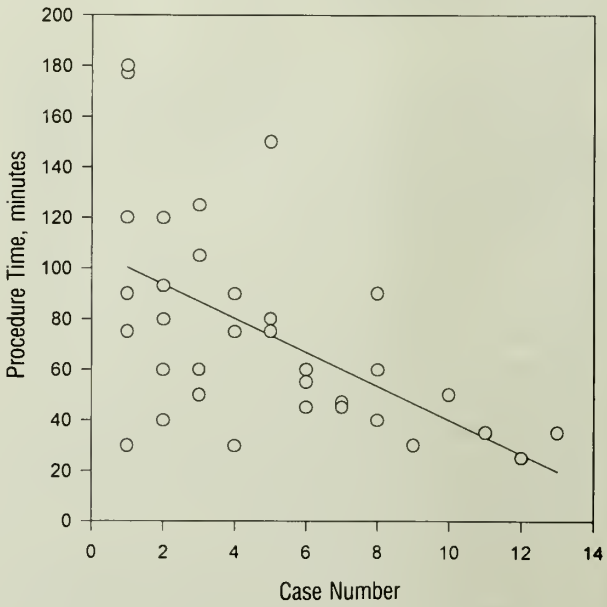

Figure 6.—The time required to do a laparoscopic jejunostomy decreases as surgeons become more experienced.

TABLE 2.—Comparison of Complications and Death in Patients Undergoing Enterostomies by Different Techniques

Enterostomy Technique	Complications, % of Patients: Operative Complications	Tube Dislodged	Convert to Laparotomy	30-Day Mortality	Reference
Percutaneous endoscopic gastrotomy	24	8	0	17	Jarnagin et al, 1992[8]
Laparoscopic gastrostomy	16	9	9	3	Duh and Way, 1993[3]; this report
Open jejunostomy	16-46	4-24	NA	21	Weltz et al, 1992[5]; Cogen et al, 1991[6]; Smith-Choban and Max, 1988[7]
Laparoscopic jejunostomy	11	14	8	11	This report

NA = not applicable

wall, may make the occurrence of volvulus less likely.

A jejunostomy catheter can be dislodged and cause a notable problem.[6] The T-fastener technique appears to offer an advantage should the catheter become dislodged. Because the T-fasteners surround the catheter site, the risk of leakage and peritonitis is minimal. Because the jejunostomy site is fixed to the anterior abdominal wall, the dislodged catheter can be replaced directly at the bedside or under fluoroscopy. Two of our patients returned after their catheters were dislodged for a few days, and the tracks had closed. A second laparoscopic jejunostomy in these two patients was easier than the initial operations because the proximal jejunum was already affixed to the anterior abdomen.

Patients who require enteral feeding by gastrostomies or jejunostomies usually have severe illness, such as end-stage cancer, neurologic deficit, and cardiopulmonary diseases, and have a high rate of mortality and morbidity (Table 2).[3,5-8] One study showed that a third of patients died within 60 days and half died within six months of the procedure, mostly of their underlying disease.[9] Another study of patients who underwent open jejunostomy showed a mortality of 21% at 30 days; most died of cardiopulmonary diseases.[5] Of our patients, 4 (11%) died within 30 days of the procedure. All had severe underlying diseases, and their jejunostomies were functioning at the time of death. Because the jejunostomies were not the cause of death, more stringent patient selection would have decreased the postoperative mortality.

When enteral feeding is required to treat or prevent malnutrition, we prefer doing gastrostomies. Percutaneous endoscopic gastrostomy can be done using local anesthesia and sedation. When a percutaneous endoscopic technique is not possible, we place the gastrostomy under laparoscopic guidance.[3] Gastrostomy has the advantage of a reservoir for bolus feeding, and a larger catheter is less likely to kink or clog and can be replaced easily.[8,10] We place jejunostomies in patients who have contraindications to a gastrostomy, such as gastroparesis, gastric outlet obstruction, or gastroesophageal reflux. These patients are at risk for aspiration if they are fed through gastrostomies.

Placing a jejunostomy laparoscopically using the T-fastener technique has advantages over alternative techniques. Open (Witzel) jejunostomy requires a laparotomy, with possible wound complications and longer postoperative recovery. Needle jejunostomy also requires a laparotomy, and the small lumen of the catheter clogs easily. Percutaneous endoscopic jejunostomy, in which a jejunostomy catheter is threaded through a gastrostomy (percutaneous endoscopic jejunostomy) catheter, has been advocated by some.[11] Its use is associated with a high rate of failure and complications, however, and has been abandoned by many endoscopists.[9,12,13]

Other alternative techniques have all been used successfully in a few patients. An endoscopy-assisted open jejunostomy has been described in which a long endoscope is passed to identify and "tent" the proximal jejunum. The jejunum is pulled through a mini-laparotomy incision, and the catheter is inserted.[14] A laparoscopically assisted open jejunostomy also has been described.[15] Other methods for laparoscopic jejunostomies require transabdominal suturing to fix the jejunum to the abdominal wall.[16-18] An interventional radiologic technique for direct percutaneous placement of a jejunostomy catheter using the Cope gastrointestinal suture anchor has also been reported.[19] The T-fastener technique is simpler to do because it requires no laparoscopic suturing or knotting and can be mastered by surgeons who are experienced in other laparoscopic procedures. It is minimally invasive and allows direct inspection of the bowel.

This prospective multicenter study showed that when done by experienced laparoscopic surgeons, laparoscopic jejunostomy using the T-fastener technique is safe and effective. Feedings can be instituted promptly, and serious complications are rare. If the jejunostomy catheter becomes dislodged, leaks do not occur, and the catheter can nearly always be replaced without a laparotomy.

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* * *

THE ACCIDENT

A dry straight road and a red Ford coupe.
Seventy into a rock that marks
the driveway of a man, who, mowing his lawn,
can only open his mouth to say "no" or "watch out,"
some word that forms a powerless O.
He stands there. The car ticks. A child's car seat sways.
A spot in the road, loaves of white bread
and diapers blown into the weeds,
and the woman wailing so
the cats in the neighborhood disappear for days.
Not until January will salt and the plow
scrape up the rubber. Mud season the oil will sink.
July they'll resurface it.

ELLEN DUDLEY©
Marlboro, Vermont

Articles

Adverse Effects of Topical Corticosteroid Use

DAVID A. FISHER, MD, *Antioch, California*

Topical corticosteroid use, a common and often efficacious therapy for a wide variety of cutaneous conditions, may have substantial adverse effects. These range from the notable nondermatologic side effects of hypothalamic-pituitary-adrenal axis suppression, Cushing's disease, femoral head osteonecrosis, and cataracts to a variety of less serious skin effects such as cutaneous tinea and contact dermatitis. The broad availability, efficacy, relative low cost, and ease of applying topical corticosteroids should not induce complacency or a cavalier attitude in prescribers. Physicians should have the same awareness of the possible side effects of topical steroid use as when prescribing parenteral medication.

(Fisher DA: Adverse effects of topical corticosteroid use. West J Med 1995; 162:123-126)

The introduction of the ultrahigh-potency topical corticosteroids has proved of important benefit for some hitherto corticoid-resistant dermatoses, but as in every new development in medicine, an adverse side to this therapeutic advance exists.

Fortunately, systemic side effects of topical corticosteroids are rare, but may occur, especially in infants[1] and elderly patients.[2(p81)] Possible systemic side effects are related directly to such factors as the application site, duration of application, potency, and occlusion of the medication.[2] The application of high-potency corticosteroids should be limited, when possible, to a twice-a-day basis for three to four weeks.[3] Longer and more frequent application of topical corticosteroids carries the risk of suppressing the hypothalamic-pituitary-adrenal axis and even producing Cushing's syndrome, especially in very young patients.[4-6] Physicians must also be aware of increased transcutaneous penetration in certain areas of the body with thin epidermis, such as the eyelids, periorbital area, axillas, crural region, and genitalia.[7] A patient with an integumentary perturbation, the quintessential example being exfoliating dermatitis, has a much greater amount of percutaneous penetration.[8] A recent report of topical clobetasol propionate-induced femoral head osteonecrosis describes additional serious systemic effects of topical high-potency corticosteroid use.[9]

Local side effects, unlike systemic ones, are relatively frequent and becoming even more so with the introduction of the ultrahigh-potency topical corticosteroids.[10] Striae distensae may develop, especially in the groin and axillas, with the prolonged application of even medium-potency corticosteroids (Figure 1).[11]

Clotrimazole and betamethasone dipropionate (Lotrisone), which can be an effective topical agent for treating intertrigo, with long-term use has the potential of rapidly inducing striae, especially in susceptible adolescents and younger adults when used more than seven to ten days in the crural, axillary, and flexural regions (Figure 2 and Figure 3). Another adverse effect that occurs more often in older persons and in young children, but that can occur in all age groups, is cutaneous atrophy with telangiectasia and stellate pseudoscars, especially with the prolonged use of the high- and ultrahigh-potency topical corticosteroids (Figures 4, 5, and 6).[12,13] Adverse effects of topical corticosteroid use on the supporting collagen stroma, by inhibiting collagen production of fibroblasts, may lead to the occurrence of purpura and induce or aggravate Bateman's senile purpura.[14] Clinicians generally should eschew the use of anything but low-potency corticosteroids on the face because of the rapid induction of erythema, corticoid rosacea, and perioral and periocular acneiform dermatoses (Figure 7).[15]

Unfortunately, the pharmaceutic industry has not always been vigilant in warning physicians concerning these possible adverse effects. An example is with mometasone furoate (Elocon), which was promoted as being safe for facial conditions, but in reality is a medium-potency steroid. Succumbing to a representative's enthusiastic sales pitch for the medication and assurances that it was safe for facial use, I produced a case of this syndrome. I have since managed several cases of mometasone-induced steroid rosacea. After complaints from me and others, the company now states that it is safe to use only for two weeks for facial dermatoses.

I strongly entreat clinicians to minimize the use of medium- and high-potency corticoids on the face of any patient. The lower-potency corticosteroids such as desonide, and even 2% to 0.5% hydrocortisone, should have adequate anti-inflammatory therapeutic benefit without the risk of producing often-difficult-to-manage steroid rosacea and erythema. Indeed, a problem with a medium- and higher-potency corticosteroid on the face is that it induces rebound erythema in which the topical corticosteroid initially causes vasoconstriction, but when

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Figure 1.—Striae occur in the groin due to the use of topical clotrimazole and betamethasone dipropionate (Lotrisone).

withdrawn, produces vasodilation higher than the baseline in a trampoline-like manner.[15] I have found a course of tetracycline or erythromycin, perhaps a short burst of intermittent parenteral corticosteroids, and time to be the only approach that benefits this most distressing condition. Topical corticosteroids can facilitate the proliferation of *Propionibacterium acnes*, and perhaps *Demodex folliculorum*, leading to an acne rosacea-like condition (Figure 7) that, fortunately, is often amenable to parenteral antibiotics coupled with topical keratolytic and antibacterial agents.[16,17] The long-term application of topical corticosteroids can induce milia in older patients.[18]

A prolonged use of topical corticosteroids on the eyelids can not only cause thinning of the eyelids but also induce open-angle glaucoma and cataracts from transpalpebral tarsal penetration.[19] Topical corticosteroids may suppress the normal cutaneous immune response to dermatophytes and thus enhance fungal infections. This can present an atypical clinical picture, to which the rubric tinea incognito has been applied.[20] I have observed cases of tinea in which betamethasone, a valuable corticosteroid moiety of Lotrisone, seemed to have a dominant effect over the antifungal aspect of the clotrimazole and worsened rather than cleared the cutaneous tinea. Cutaneous dermatophyte infections

TABLE 1.—*Possible Adverse Effects of Topical Corticosteroid Use*

Systemic Absorption	
Hypothalamic-pituitary-adrenal axis suppression	
Cushing's disease	
Femoral head osteonecrosis	
Local Effects	
Striae distensae	Milia
Cutaneous atrophy	Cataracts
Stellate pseudoscars	Tinea
Telangiectasia	? Candidiasis
Purpura	Scabies
Erythema	Hypertrichosis
Rosacea	Hypopigmentation
Acneiform dermatoses	Contact dermatitis
Rebound erythema	Tachyphylaxis
Demodicidosis	

should be treated only with a topical fungicide. A clinical study of 176 patients with potassium hydroxide and fungal culture-proven tinea pedis unequivocally documents the superiority of a single antifungal topical agent, in this instance naftifine hydrochloride, over the antifungal corticosteroid combination of clotrimazole and betamethasone proprionate.[21] The decision whether to use oral antifungal therapy is a matter of clinical judgment. Topical corticosteroid use may promote cutaneous candidiasis, although experimental proof of this is lacking.[22] Local steroid use may induce atypical or extensive crusted scabies.[23] Hypertrichosis is a rare side effect of the long-term use of topical steroids. When it does occur, it is most prevalent on the face and ears.[24] Hypopigmentation from high- and ultrahigh-potency steroids is a possible consequence when used on a dark-skinned person.[25]

Reports of cases of type IV allergic contact dermatitis due to local steroid use are increasing.[26] The rash may be chronic, erythematous, edematous, papular, and at times scaly, as opposed to the usual microvesicular eczema of acute contact dermatitis. This somewhat alarming development has not been totally elucidated,

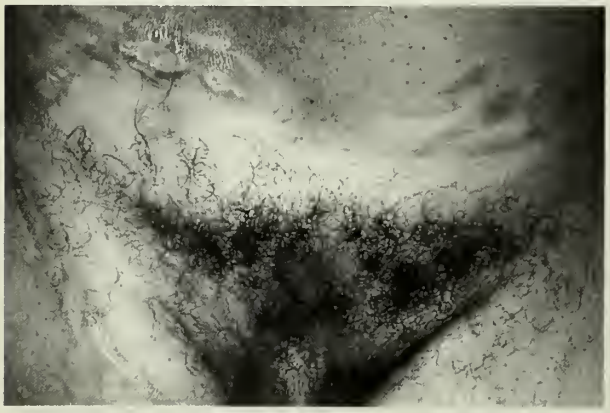

Figure 2.—Striae and skin breakdown due to the use of topical medium-potency corticosteroids are shown.

Figure 3.—Higher-potency topical corticosteroid use produced striae on the arms.

Figure 4.—Cutaneous atrophy is shown from intralesional corticosteroid therapy.

Figure 6.—Telangiectasia of the nose has occurred from the use of topical medium-potency corticosteroids.

but is the cause of some cases of corticosteroid-resistant dermatitis.[27] Unfortunately, the screening corticosteroids tixocortol pivalate and budesonide are unavailable for patch tests in the United States because of the Food and Drug Administration (FDA) requirement that allergens for patch testing are a medication and must be FDA-approved.[28] The use of these chemicals does not identify all cases of corticosteroid hypersensitivities, but according to a recent report, it identifies more than 80% of them.[29]

Practitioners should also be mindful of the possibility of allergic contact dermatitis due to certain excipients of varying concentrations in topical corticosteroid preparations. These may be type IV delayed-hypersensitivity sensitizers, such as lanolin, paraben, and quaternium 15, or chemicals capable of producing an immediate contact urticaria, either on a nonimmunologic histamine-releasing basis or from an immunoglobulin E-mediated, type I immediate reaction.[30] The preservatives sorbic acid, benzoic acid, and formaldehyde are examples of such contact urticaria inducers.[31]

Topical corticosteroids may induce tachyphylaxis with extended use.[32] This occurs most often in patients with psoriasis. This is an another reason why it is recommended that the frequency of the application of ultrahigh-potency topical corticoids be reduced after the first two to three weeks to no more than four or five times a week.

Physicians are always mindful of the possible adverse systemic effects of the use of parenteral medications. We should be no less mindful of the possible undesirable side effects of this therapeutically valuable topical medicament.

Acknowledgment

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Figure 5.—Higher-potency topical corticosteroid use produced cutaneous atrophy with resultant skin fragility and erosions.

Figure 7.—The photograph shows topical corticosteroid-induced acne rosacea.

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Articles

California Physicians' Willingness to Care for the Poor

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Although generalist physicians appear to be more likely than specialists to provide care for poor adult patients, they may still perceive financial and nonfinancial barriers to caring for these patients. We studied generalist physicians' attitudes toward caring for poor patients using focus groups and used the results to design a survey that tested the generalizability of the focus group findings. The focus groups included a total of 24 physicians in 4 California communities; the survey was administered to a random sample of 177 California general internists, family physicians, and general practitioners. The response rate was 70%. Of respondents, 77% accepted new patients with private insurance; 31% accepted new Medicaid patients, and 43% accepted new uninsured patients. Nonwhite physicians were more likely to care for uninsured and Medicaid patients than were white physicians. In addition to reimbursement, nonfinancial factors played an important role in physicians' decisions not to care for Medicaid or uninsured patients. The perception of an increased risk of being sued was cited by 57% of physicians as important in the decision not to care for Medicaid patients and by 49% for uninsured patients. Patient characteristics such as psychosocial problems, being ungrateful for care, and noncompliance were also important. Poor reimbursement was cited by 88% of physicians as an important reason not to care for Medicaid patients and by 77% for uninsured patients. Policy changes such as universal health insurance coverage and increasing the supply of generalist physicians may not adequately improve access to care unless accompanied by changes that address generalist physicians' financial and nonfinancial concerns about providing care for poor patients.

(Komaromy M, Lurie N, Bindman AB: California physicians' willingness to care for the poor. West J Med 1995; 162:127-132)

Increasing the availability of health insurance coverage appears necessary but insufficient to improve access to care for poor patients. Studies of expanding Medicaid eligibility have been unable to show consistent improvements in access to care or in health outcomes.[1-3] Many health policy analysts have suggested that access to care can be improved by linking expansion of health insurance coverage with a shift in the delivery of care from specialist to generalist physicians.[4-6]

Indirect evidence suggests that generalist physicians are more likely than specialists to provide care for poor patients. Generalist physicians are more likely than specialists to practice in rural areas and inner cities,[7] their fees are lower, and they see more patients per hour than specialists.[8] They report that they devote a somewhat greater percentage of their practice to Medicaid patients than do specialists.[9]

It is unclear, however, whether these observed practice differences reflect physician attitudes that will guarantee improved access to care for poor patients if the physician workforce shifts from specialist to generalist. Analysts have concluded that successful reform will need to address nonfinancial as well as financial barriers to care.[10,11] Physicians' attitudes or beliefs may pose such nonfinancial barriers; for example, physicians might be reluctant to care for patients from a socioeconomic class or cultural background different from their own. A study of the willingness of family physicians to provide obstetric care for Medicaid patients suggested that the fear of being sued and the perception that Medicaid patients are noncompliant were both important factors in the decision to discontinue obstetric care for these patients.[12] A study of pediatricians found that broken appointments and "the type of patient" eligible for Medicaid were perceived as

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important problems with the Medicaid program.[13]

To learn more about generalist physicians' attitudes toward caring for low-income adult patients and the financial and nonfinancial factors that affect their attitudes, we conducted structured small-group interviews—focus groups—and a survey of generalist physicians in California. We studied whether physicians are willing to accept patients who lack private insurance into their practice, and how they decide whether to provide care for these patients.

Sample and Methods

We conducted focus groups with physicians and then used these findings to design a physician survey. Focus groups are a qualitative research method in which a small number of study subjects participate in structured group interviews.[14] The open-ended nature of the questions posed in the focus groups makes this a useful technique for understanding the range of physician attitudes and motivations.[15] Because it is difficult to generalize from focus group data, we conducted a survey of a random sample of primary care physicians in California to examine how broadly generalizable the focus group findings were. The study protocol was approved by the University of California, San Francisco, Human Subjects Committee.

We formed four focus groups with a total of 24 practicing generalist physicians. Letters of invitation were sent to the general internists and family and emergency physicians on the admitting staff of one hospital in each of four northern California communities. Participants were enrolled in the order in which they responded up to a total of seven per group. The hospitals were a semiurban public teaching hospital, an urban private teaching hospital, an urban private nonteaching hospital, and a rural private nonteaching hospital. Physicians were told only that we were studying physician decision making and were offered $100 to participate. Discussions were facilitated by two of us (M.K. and N.L.), who are general internists and have been trained in focus group facilitation. The groups each lasted 60 to 90 minutes. Among the 24 physicians, 22 were men; 13 were internists, 7 were family physicians, and 4 were emergency physicians.

Using a script of prepared questions, we asked physicians how patients' social and economic status influenced their clinical practice and decision making. We investigated how they decide whether to care for uninsured and Medicaid patients; and if they choose not to, we explored their reasons and strategies for avoiding these patients.

The sessions were audiotaped and transcribed. Patterns and trends of responses were established through a content analysis of the data that entailed systematic coding. Each investigator analyzed the content of the groups, and the analyses were compared and integrated.[16]

To ascertain the generalizability of the findings from the focus groups, we surveyed a random sample of 80 California general internists, 80 family physicians, and 80 general practitioners in active practice. Participants were chosen from the current roster of California physicians from the American Medical Association Physician Masterfile. The Masterfile includes physicians who are not members of the American Medical Association. Participants were initially mailed the survey in April 1993 and were informed that on receipt of their survey, their name would be entered into a drawing for one of two continuing medical education tuition vouchers worth $500. Within a month, nonresponders were sent a reminder postcard and a second copy of the survey. Physicians who still had not responded were contacted by telephone or by a visit to their office.[17] We attempted to verify the addresses of nonresponders through telephone information, an inquiry to the state licensing board, and finally with a postcard asking office staff to confirm whether the physician was actively practicing in California. Physicians were considered ineligible if we learned that they were not a general internist, general practitioner, or family physician currently practicing in California.

The survey was a written, closed-ended questionnaire developed from a review of the literature and from the focus group findings. Physicians were asked whether they were accepting new patients with different insurance types; if they were not, why not; the insurance status of patients in their practice; and factors in their practice setting that might influence their decision to accept patients with different types of insurance.

The survey was analyzed in two stages. Demographics and practice characteristics were compiled for all respondents. Physicians who said that they were accepting patients with private fee-for-service or managed care insurance were asked whether they were accepting new patients with Medicaid and with no insurance. Physicians who accepted Medicaid or uninsured patients, or both, were then compared with those who accepted neither, to see whether they differed with regard to physician demographics or practice setting (Fisher's exact test). Race was dichotomized into white (non-Hispanic) and nonwhite (plus Hispanic). Family physicians and general practitioners were combined for analysis because many physicians listed as general practitioners in the American Medical Association Masterfile identified themselves as family physicians on the survey. A logistic model designed to predict physician acceptance of Medicaid and uninsured patients was constructed using individual variables that were significant at the $P = .1$ level in the univariate analysis: physician race, practice location, and hospital type. Physicians' reasons for not accepting patients were examined separately for Medicaid and uninsured patients; because these were not mutually exclusive—physicians could accept both, one, or neither, for example—comparative statistical analysis was not done.

Because the survey results paralleled the attitudes we heard discussed in the focus groups, we have chosen to present them together using illustrative quotes from the focus groups to highlight the survey data.

TABLE 1.—*Characteristics of Physicians Who Accept Medicaid or Uninsured Patients*

Physician Characteristic	No. Accepting Medicaid or Uninsured Patients/ No. in Category (%) n = 95	P Value
Race*		
White	30/56 (54)	
Nonwhite	30/39 (77)	.02
Hospital type†		
Nonpublic	39/67 (58)	
Public	19/24 (79)	.05
Practice location		
Urban	49/82 (60)	
Rural	11/13 (85)	.08
Sex		
Male	48/78 (62)	
Female	12/17 (71)	.34
Specialty		
General internist	28/46 (61)	
Family physician or general practitioner	32/49 (65)	.41
Training		
United States	40/65 (62)	
Foreign	20/30 (67)	.40
Years since graduation		
≤ 10	14/20 (70)	
> 10	46/75 (61)	.33

*Table excludes 29 physicians who were accepting no new patients.
†The numbers add up to less than 95 because of skipped answers.

Results

The survey was mailed to 240 physicians. Of these, 37 were found to be ineligible because they had retired, moved out of state, were in another specialty, or were deceased. In addition, we considered 26 physicians ineligible because five or more attempts to locate them through mail, telephone, and the physician licensing board were unsuccessful. We received responses from 124 of the 177 remaining physicians (70%). The respondents did not differ from the nonrespondents with respect to age, sex, specialty, or years in practice. Respondents were predominantly white (63%), male (78%), and trained at medical schools in the United States (73%). Of our respondents, 60% admitted patients primarily to private hospitals, 24% to public hospitals, and 9% to health maintenance organization hospitals.

Providing Care for Medicaid and Uninsured Patients

Of the 124 physician-respondents, 95 (77%) said they accept new patients with private insurance (fee-for-service or managed care); 31% accept new Medicaid patients, and 43% accept new uninsured patients who are unable to pay full fee. Physicians who said that they accept new uninsured or Medicaid patients also reported a significantly greater percentage of such patients in their practices ($P < .001$). These low rates of providing care for Medicaid and uninsured patients occur despite the fact that physicians in general rate the number who are willing to care for such patients in their area as inadequate. When asked about the adequacy of the supply of primary care physicians in their communities, 100 respondents (81%) reported that there were far too few or somewhat too few providing care to Medicaid patients, and 109 (88%) said the same was true for uninsured patients.

These findings reinforced focus group comments. One focus group physician remarked:

"I doubt very much whether there's any physicians taking new Medicaid patients in [our community]; and there probably hasn't been for many years."

Several physician characteristics were related to the acceptance of new Medicaid or uninsured patients (Table 1). In univariate analysis, nonwhite physicians and those who admit patients primarily to public hospitals were more likely than their counterparts to accept new Medicaid or uninsured patients. Rural physicians tended more than nonrural physicians to accept new Medicaid or uninsured patients. In a simultaneous logistic regression analysis, physician race (nonwhite) remained a significant predictor of accepting Medicaid and uninsured patients ($P = .05$). There continued to be a trend for rural physicians to do so ($P = .08$), although admitting to a public hospital was no longer a significant predictor ($P = .16$).

In the focus groups, physicians described several strategies to avoid caring for uninsured and Medicaid patients. Some physicians refused all patients without private insurance either in the hospital or as outpatients. Another strategy was to arrange for residents to provide outpatient care for these patients. Other physicians transferred all uninsured patients to public hospitals. A final strategy was to agree to care for uninsured and Medicaid patients as inpatients or in the emergency department, but not to provide follow-up outpatient care. This strategy was articulated thus:

"The best strategy—no, I'm sorry, MY *strategy—is I don't see them in my office."*

In some settings, on-call physicians are also expected to provide follow-up care for patients who are seen in the emergency department but not admitted. An emergency physician described the situation in one of the communities where she worked:

"We'd assign them to the family physician on call, and my understanding when I started there was that they were obligated, the staff, to see that patient once, but they didn't have to see them on an ongoing basis. . . . And what was happening was the office people were screening them. They'd call and they'd say what kind of insurance they had, and try to make an appointment to follow up. And if they told them they had Medicaid or were unfunded, the clerk said, 'Sorry, we can't see you.' Boom. And they never got any further than that."

TABLE 2.—*Physicians' Reasons for Not Providing Care to Medicaid and Uninsured Patients*

	Physicians Not Accepting Medicaid n = 58			Physicians Not Accepting Uninsured n = 43		
Reason	*No.*	*%*	*(95% CI)*	*No.*	*%*	*(95% CI)*
Reimbursement						
Inadequate	51	88	(80-96)	33	77	(64-89)
Difficulty providing adequate care						
Burdensome paperwork	43	74	(63-85)	9	21	(9-33)
Difficulty obtaining specialty consultations	40	69	(57-81)	28	65	(51-79)
Difficulty obtaining tests	20	35	(22-47)	28	65	(51-79)
Perceived increased malpractice risk						
Increased risk of being sued	33	57	(44-70)	21	49	(34-63)
Patient characteristics						
Psychosocial problems	24	41	(29-54)	20	47	(31-61)
Ungrateful for care	21	36	(24-48)	13	30	(16-44)
Noncompliant	36	62	(50-75)	17	40	(25-54)

CI = confidence interval

Reasons for Avoiding Medicaid and Uninsured Patients

In both the focus groups and the survey, physicians' reasons for avoiding Medicaid and uninsured patients fell into four broad categories: inadequate reimbursement, difficulty providing adequate care, perception of increased malpractice risk, and patient characteristics (Table 2).

Reimbursement

When survey physicians were asked why they did not accept patients with Medicaid, 51 (88%) cited poor reimbursement. Among those not accepting uninsured patients, poor reimbursement was cited by 33 (77%) (Table 2). This finding corroborated focus group data. For example, a physician said:

"I don't take any new Medicaid patients, and my colleagues are all doing the same thing now . . . and it is mostly for financial reasons. Our reimbursement goes down, our census goes up, and you find yourself working harder and not making ends meet the way you have."

Difficulty Providing Adequate Care

Survey physicians reported that difficulty in providing adequate care for Medicaid and uninsured patients influenced their decision not to provide care for these patients (Table 2). Burdensome paperwork and difficulty obtaining specialty consultations were important reasons for avoiding Medicaid patients, whereas difficulty obtaining specialty consultations and diagnostic tests were important reasons for avoiding uninsured patients.

In the focus groups, physicians described their frustration at trying to obtain needed services for their patients who lack private insurance.

"The problem of the unfunded patient is really very, very difficult for the private physician. . . . I would be more than happy to treat these people, but if they need referral, or if they need lab work, or if they need x-rays . . . these people will either tell you that they don't have the money to pay for it [or] they don't want to pay for it, and you're forced . . . into practicing poor medicine."

A physician at another hospital remarked:

"I do feel bad when the Medicaid patients that I am taking care of . . . need to see a specialist. It's hard to find somebody else who will take them."

Survey physicians who reported that their hospital had a policy against admitting uninsured patients were less likely than those whose hospital had no such policy to accept uninsured patients into their practice ($P < .01$). Two focus group physicians discussed the influence of their hospital's admission policy:

First physician: *"I wouldn't admit anyone who had no insurance."*

Second physician: *"The hospital won't take them, unless they're too unstable."*

First physician: *"No, they couldn't get in the door, anyway."*

Increased Malpractice Risk

The perception that they were more likely to be sued was cited as an important reason for avoiding poor patients by 33 of the physicians who did not accept Medicaid (57%) and 21 of those who did not accept uninsured patients (49%; Table 2).

In the focus groups, physicians expressed three areas of concern about increased malpractice risk. Many thought that Medicaid patients were actually more likely to bring lawsuits against physicians than were other patients.

"Your risk of being sued for malpractice is greater. [Medicaid patients] have multiple problems you don't know anything about."

Some physicians were aware that studies have shown that this is not the case,[18,19] but thought that the presence of any substantial risk of being sued was unacceptable when providing care to patients who are not privately uninsured.

"I understand that you're actually less likely to be sued by [Medicaid patients]; but you can be sued by them and always really resent it when you're taking care of somebody for essentially nothing and you get nailed."

Others thought they were particularly vulnerable to being sued because difficulty obtaining tests and consultations for poor patients caused them to provide substandard medical care.

Patient Characteristics

In the survey, psychosocial problems and patient noncompliance were cited as important reasons for avoiding both Medicaid and uninsured patients (Table 2). This echoed attitudes expressed in the focus groups. One physician said:

"They are more difficult to take care of . . . they have lots of social and medical problems, they are more

difficult in terms of compliance, they have drug habits, things like that."

In addition, 36% of survey physicians felt that Medicaid patients were ungrateful for care. A focus group physician described caring for Medicaid patients:

"You just don't get the positive feedback and reward for trying to make these people well, because they can sabotage and destroy things; usually not deliberately, but they just. . . . They're hard to work with. They're hard to help. And you get tired."

Another physician in the same group disagreed:

"I have a handful of Medicaid patients in my practice, and they're very appreciative. They're appreciative overall of what they get, and they recognize that there are major limitations to what I can do for them."

Discussion

Nearly half the physicians we surveyed said they provide care for Medicaid or uninsured patients despite many financial and nonfinancial issues that make this difficult. Yet most thought that the supply of physicians who care for uninsured and Medicaid patients in their community was inadequate. We have identified a number of financial and nonfinancial factors that discourage physicians from caring for these patients. Efforts to reform health care would need to address these factors to increase the availability of health care for the poor.

Inadequate reimbursement is the reason physicians cited most commonly for choosing not to care for Medicaid and uninsured patients. Generalist physicians cannot be expected to assume responsibility for large numbers of poor patients if their reimbursement does not meet or only marginally exceeds their operating costs. Although health care reform efforts offering universal insurance coverage would improve financial access to health care, they might not eradicate financial barriers. Just as existing Medicaid programs have often been unsuccessful in providing the poor with financial access to care, a low-cost plan under a managed competition style health care reform plan might provide reimbursement that physicians would regard as inadequate compared with the reimbursement they receive for other patients. Rules that ensure that health plans cannot refuse coverage to patients may not deter physicians who function as independent providers from excluding patients because of inadequate reimbursement. If large differentials in reimbursement exist between health plans, or if some Americans continue to be insured by low-reimbursing Medicaid programs, poor patients are likely to face continued financial barriers to care even if comprehensive health care reform occurs in the future. Patients' Medicaid status or membership in another low-paying health plan could also stigmatize them as undesirable to some physicians for nonfinancial reasons and allow physicians to avoid them.

Three categories of nonfinancial issues played an important role in physicians' decisions not to care for Medicaid and uninsured patients: difficulty providing adequate care, fear of increased malpractice risk, and perceived patient characteristics.

Physicians identified several ways in which they had difficulty providing adequate care for poor patients. Burdensome paperwork, in addition to adding to the cost of care, was seen as a substantial diversion from patient care. Physicians were frustrated by difficulty obtaining diagnostic tests and specialty consultations and felt unable to provide care consistent with community standards. These findings are consistent with a recent study that found that when poor patients are admitted to hospital, they are more likely than others to receive substandard care.[20] Both patients and physicians suffer when substandard care is provided, and some physicians simply opt not to care for these patients rather than face this alternative. Even with health care reform that provided universal financial coverage, these problems would persist, and generalist physicians would not be able to solve these problems on their own. Specialists must be willing to accept appropriate referrals to help ensure that poor patients receive adequate care. Adequate reimbursement, coverage of laboratory tests and outpatient services, tort reform, and the elimination of burdensome paperwork are also needed.

Physicians were deterred from caring for poor patients by undesirable personal characteristics that they attributed to these patients. Addressing physicians' attitudes toward personal characteristics of poor patients is a challenging problem. Medical schools can attempt to recruit applicants who have a sense of responsibility toward the care of poor and underserved groups.[21,22] Our finding that nonwhite physicians are more likely than others to care for Medicaid and uninsured patients suggests that recruiting greater numbers of nonwhite physicians could be important for overcoming nonfinancial access barriers. Medical training sites can be relocated to high-need rural and inner-city areas to help accustom physicians to the goal of meeting the needs of a community.[22-24] The clinical curriculum can be restructured to focus more on skills needed to deal effectively with patients' social and psychological problems.[25] When better prepared, physicians may come to view these problems as challenging rather than undesirable. Finally, generalist physicians cannot carry the burden of medical, psychiatric, and social services for these patients; ready access to mental health and social services is critical to improving health care for poor patients.

Our study is limited by our reliance on physician self-report. Focus groups are useful for revealing attitudes and motivations, but they may present an overly negative picture of physician attitudes because group consensus may be swayed by extreme opinions. On the other hand, physicians are known to overestimate the amount of care they provide to low-income patients when they are asked in a survey format.[26] We used the combination of focus groups and a written survey to try to capture a balanced picture of generalist physicians' attitudes.

Even health care reform that provides universal coverage and increases the proportion of generalist physicians might not adequately improve access to care unless these are accompanied by changes that address generalist physicians' financial and nonfinancial concerns about providing care for poor patients.

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Conferences and Reviews

Fulminant *Mycoplasma pneumoniae* Pneumonia

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The frequency of fulminant pneumonia due to *Mycoplasma pneumoniae* is relatively rare despite the high prevalence of *Mycoplasma* species infection in the general population. We recently encountered such a case and have reviewed the English-language literature on cases of *M pneumoniae* pneumonia that have resulted in respiratory failure or death. Due to host factors or on epidemiologic grounds, fulminant cases seem to be more common in young healthy adults, in males, and possibly in smokers among the 46 patients we found. An enhanced host cellular immune response may be responsible for the development of severe cases. A spectrum of small airways disease is characteristic, including cellular bronchiolitis and bronchiolitis obliterans with and without organizing pneumonia. Based largely on anecdotal experience, corticosteroid use may be salutary in patients with respiratory failure. For reasons that are not well known, the incidence of pulmonary thromboembolism is increased in fatal cases.

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The vast spectrum of diseases caused by *Mycoplasma pneumoniae* includes pharyngitis, sinusitis, tracheobronchitis, pneumonia, myocarditis, pancreatitis, hepatitis, arthritis, and meningoencephalitis. Associated findings are equally diverse and include intravascular hemolysis and coagulation and skin eruptions.[1-5] The protean respiratory complications of *M pneumoniae* pneumonia have included cases of cellular bronchiolitis,[6] bronchiolitis obliterans with or without organizing pneumonia,[6-8] bronchiectasis,[9] pneumatoceles,[10] Swyer-James syndrome,[11] pleural effusion,[2,12] the adult respiratory distress syndrome,[13,14] pulmonary embolism,[15] chronic interstitial fibrosis,[16,17] and lung abscess.[18]

As noted in a review of human mycoplasmal diseases,[3] the current literature stresses the benign and often subclinical nature of such infections, even when pneumonia has occurred. Indeed, it is estimated that clinically apparent pneumonia develops in only 3% to 10% of those infected with *M pneumoniae*[3] and that less than 5% of cases of pneumonia are severe enough to require admission to a hospital.[1,19]

A singular case of severe respiratory insufficiency in a previously healthy young man with *M pneumoniae* pneumonia was recently encountered. A literature search was undertaken to characterize patients in whom this disorder resulted in hypoxic respiratory failure or death. This information is reported because it emphasizes that life-threatening, defined here as "fulminant," *M pneumoniae* infections attack mostly previously healthy people, that empiric antibiotic therapy for community-acquired pneumonia should include coverage for both "typical and atypical" organisms, and that thromboembolism is common in fatal cases.*

Case Presentation

The patient, a 19-year-old male college student who was previously in excellent health, had myalgias eight days before admission, followed by fever, chills, and a nonproductive cough. Over the next few days, he was twice seen in the emergency department and was treated symptomatically for a presumed viral upper respiratory tract infection. He was subsequently admitted because of progressive shortness of breath; on examination, the temperature was 38.1°C, pulse 140 per minute, blood pressure 150/70 mm of mercury, and respiratory rate 32 per minute. Notable findings included cyanosis with bilateral crackles on lung examination. The sputum was mucoid and blood-tinged, and Gram's stain showed abundant neutrophils without a predominant organism. The leukocyte count was 5.6×10^9 per liter (5,580 per mm^3) with 0.80 neutrophils (80%), 0.14 lymphocytes (14%), and 0.03 monocytes (3%); the hemoglobin level was 141 grams per liter (14.1 grams per dl), and the platelet count was 224×10^9 per liter (224,000 per mm^3). The serum sodium level was 128 mmol per liter, and the phosphorus level was 0.52 mmol per liter (1.6 mg per dl). Arterial blood gas values with the patient breathing room air at 2,135 m (7,000 ft) elevation were a pH of 7.46, P_{CO_2} 28 mm of mercury, P_{O_2} 31 mm of mercury, and an oxygen

*See also the editorial by G. H. Cassell, PhD, "Severe Mycoplasma Disease—Rare or Underdiagnosed?" on pages 172-175 of this issue.

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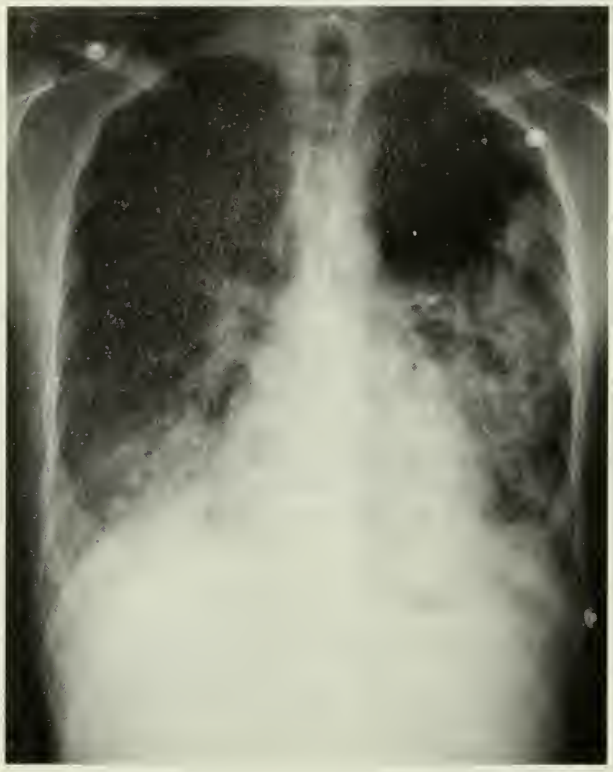

Figure 1.—The admission chest radiograph of the young man with fulminant *Mycoplasma pneumoniae* pneumonia shows diffuse alveolar infiltrates, particularly in the lower lung fields.

saturation of 0.62 (62%). A chest roentgenogram showed diffuse air-space consolidation largely in the lower lung fields (Figure 1).

Although a four-drug antibiotic regimen was begun that included erythromycin, 500 mg given four times a day intravenously, hypercarbia and progressive hypoxemia developed, necessitating mechanical ventilation on the fifth hospital day. A bronchoalveolar lavage specimen was negative for *Pneumocystis carinii*, and all antibiotics except the erythromycin were discontinued. Blood and sputum cultures, human immunodeficiency virus antibody test, and paired serologic titers for *Legionella pneumophila*, respiratory syncytial virus, adenovirus, influenza types A and B, and parainfluenzae types 1, 2, and 3 were all negative. The complement fixation titer for *M pneumoniae* rose from 1:128 to 1:512, and the cold-agglutinin titer rose from 1:64 to 1:2,048 over a four-day interval. He had a progressively favorable course, and the endotracheal tube was removed after five days of mechanical ventilation. He was discharged to complete a three-week course of erythromycin and has recovered without sequelae.

Methods

A MEDLINE search in the English-language literature was undertaken for the period 1966 to 1991 using the following four paired words: "*Mycoplasma pneumoniae*" paired with "artificial respiration," "respiratory failure," "review," and "deaths." The bibliography of relevant articles was reviewed for all fatal and "severe" cases and those requiring lung biopsies. In addition, prospective studies of community-acquired pneumonia in patients requiring hospital admission, with each study comprising more than 100 patients, were reviewed for cases of fulminant *M pneumoniae* pneumonia and for its frequency. In suitable pneumonia studies, the mortality rate for *M pneumoniae* pneumonia was compared with the total mortality rate for inpatient pneumonia. Criteria for respiratory failure included endotracheal intubation or "respiratory failure" as noted by the authors, a Pa_{O_2} of less than 50 mm of mercury with the patient breathing room air, or a clinical diagnosis of adult respiratory distress syndrome or its pathologic equivalent, "diffuse alveolar damage."

Cases Excluded

A total of 42 cases were excluded from the review: 5 cases of respiratory failure were excluded because of mixed infections.[5,20-22] The cases of 13 patients with "severe" *M pneumoniae* infections were excluded because of an absence of objective criteria for respiratory failure.[23-26] Three patients with Down syndrome, one of whom died and the other two had "profound" hypoxia[27]; three patients with adult respiratory distress syndrome[5,19]; four patients from a community-acquired pneumonia study who died[28]; and nine patients with a Pa_{O_2} of less than 60 mm of mercury[27] were all excluded because of inadequate information about the patients and their courses. Three cases of respiratory failure were rejected because the laboratory diagnoses were based on cold-agglutinin titers alone.[29] Two cases were excluded because of contradictory statements regarding mechanical ventilation requirements.[30]

Results

In the 13 inpatient, prospective studies of community-acquired pneumonia analyzed,[28,31-42] *M pneumoniae* accounted for 0.7% to 18% (mean, 8%) of these presumably more seriously ill patients treated in hospital. In 12 of the evaluable studies,[28,31-37,39-42] the average total mortality rate for community-acquired pneumonia was 12% (range, 2% to 24%), whereas the mortality rates for *M pneumoniae* pneumonia in the two studies[28,40] that reported such deaths were 5% (4/81) and 3% (1/30), respectively.

From our review of fulminant cases of *M pneumoniae* pneumonia, three categories of patients' outcome are recognized (Tables 1, 2, and 3),[43-64] namely nonfatal respiratory failure (26 cases), fatal respiratory failure (13 cases), and fatal without respiratory failure (7 cases). Although many patients in the third group were undoubtedly endotracheally intubated, if respiratory failure was not noted before their cardiopulmonary arrest, they were included in the "without respiratory failure" group.

Nonfatal Respiratory Failure

The average age of the 26 patients summarized in Table 1 was 35 years. Most patients (23 [88%]) were previously healthy. Of the 19 male patients, 12 (63%) required mechanical ventilation compared with 2 of the 7 female patients (28%); in 2 patients, 1 male and 1 female,

TABLE 1.—*Nonfatal Respiratory Failure*

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication or Biopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
1.....	6	M	Acute lymphocytic leukemia	CA <1:8→1:128; pos throat culture	Erythromycin (14/4)	Open lung biopsy: cellular bronchiolitis	No	Pco_2 30; Po_2 49	Ganick et al, 1980[43]
2.....	16	M	- -	CA 1:256→1:512→1:32; CF 1:2,048→1:4,096	Erythromycin (10/1); steroids (13/4)	ARDS	Yes	Po_2 35	Dixon, 1981[14]
3.....	18	M	Hemoglobin SC	CF 1:32→1:128	Erythromycin (6/2)	Hemolytic anemia; pleural effusion	Yes	- -	Solanki and Berdoff, 1979[12]
4.....	20	M	- -	CF 1:4→1:64; pos throat culture	Tetracycline (?/10)	- -	No	- -	Armstrong, 1969[44]
5‡.....	21	F	- -	CF <1:8→≥1:256; CA neg →1:512	Erythromycin (14/12)	Tube thoracostomy for pleural effusion	No	Po_2 50	Gump and Hawley, 1976[45]
6.....	24	F	- -	CF 1:8 → 1:128	Tetracycline (2/1); steroids (2/1)	- -	No	Po_2 40-50	Mlczoch and Witek, 1976[46]
7.....	25	M	- -	CF 1:4 → > 1:128	Erythromycin (10/8); steroids (11/9)	Pleural effusion	No	Po_2 32-43	Noriega et al, 1974[47]
8.....	25	M	--	CF < 1:4 → 1:16	Chloramphenicol (?/8)	ARDS; open lung: "pneumonitis"	Yes	- -	Fischman et al, 1978[13]
9.....	27	M	Smoker	CF 1:128 → 1:64; CA 1:512	Tetracycline and steroids (13/3)	"Bronchiolitis"	No	Pco_2 71; Po_2 39	Zack and Kazemi, 1973[48]
10.....	30	M	- -	CF 1:8 → 1:64	Erythromycin (?/?)	ARDS; open lung: diffuse alveolar damage, bronchiolitis	Unclear	- -	Rollins et al, 1986[6]
11.....	30	M	- -	Unclear	- -	Pneumothorax; hemolysis	Yes	- -	Marrie, 1993[22]
12.....	32	F	- -	CF 1:16 →> 1:256	Erythromycin (14/11)	- -	Yes	Pco_2 70 → 100; Po_2 45 (10 liters)	Teres et al, 1973[49]
13.....	32	M	Smoker	CF 1:32→1,024; CA 1:256	Chloramphenicol (7/2)	- -	Yes	Po_2 44	Cockcroft and Stilwell, 1981[50]
14.....	33	M	- -	CF 1:64→ 1:256; CA 1:512	Tetracycline and steroids (?/?)	- -	No	Po_2 40	Mlczoch and Witek, 1976[46]
15‡....	36	M	- -	CF 1:64→1:2,048; CA 1:256	Tetracycline (14/4)	↑Liver function test values	No	- -	Fraley et al, 1979[8]
16.....	37	M	Smoker	CF 1:256→1:128; CA 1:512	Erythromycin (16/6); steroids (4→ 6th hosp day)	Open lung: BO with confluent nodular infiltrate (BOOP)	Yes	Po_2 28	Coultas et al, 1986[7]
17.....	41	M	- -	Unclear	- -	Guillain-Barré syndrome	Yes	- -	Marrie, 1993[22]
18.....	45	F	Smoker	CF < 1:8→1:2,048; CA < 1:8→ 1:256	Tetracycline (6/2)	Tracheostomy	Yes	- -	Gump and Hawley, 1976[45]
19‡....	48	F	- -	Pos sputum culture	Erythromycin (7/4)	- -	No	Po_2 60 (5 liters)	Gump and Hawley, 1976[45]
20.....	48	M	Smoker	CF 1:8→ 1:256; CA 1:160; pos sputum culture	Tetracycline and steroids (≥10/?)	Hemolytic anemia; open lung: BOOP	Yes	- -	Fraley et al, 1979[8]
21.....	50	F	- -	CF 1:1,280	Tetracycline (9/6); steroid as outpatient	Myocarditis; hemolytic anemia; 49-day hosp stay	No	Pco_2 49 Po_2 38	Holt et al, 1977[51]

(continued on next page)

Table 1 continued from previous page

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication or Biopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
22.....	52	M	- -	CF < 1:4→ > 1:128	Tetracycline (?/30)	ARDS; 69-day hosp stay	Yes§	- -	Fischman et al, 1978[13]
23.....	62	M	Chronic bronchitis	CF 1:40 → 1:160	Erythromycin (?/?)	Pancreatitis; diabetes mellitus	Yes	Po_2 27	Mardh and Ursing, 1974[52]
24.....	65	F	- -	CF 1:8 → 1:64; CA 1:64 → 1:256	Erythromycin (?/?)	Renal failure; open lung: BOOP	Unclear	- -	Rollins et al, 1986[6]
25.....	71	M	- -	CF 1:2,048 →1:8,192; CA 1:128	Tetracycline and erythromycin (10/1)	↑ Liver function test values	Yes	Po_2 53 (↑↑ Fio_2)	Cockcroft and Stilwell, 1981[50]
26‡....	19	M	- -	CF 1:128 → 1:512; CA 1:64 → 1:2,048	Erythromycin (8/1)	- -	Yes	Pco_2 25; Po_2 31	Present case

ARDS = adult respiratory distress syndrome, BO = bronchiolitis obliterans, BOOP = BO with organizing pneumonia, CA = cold agglutinin (immunoglobulin M), CF = complement fixation (immunoglobulin G), Fio_2 = fractional concentration of supplemental oxygen, hosp = hospital, neg = negative, pos = positive, ? = not reported or unable to derive, ↑ = elevated

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy begun.

‡The patient is a nonsmoker.

§The patient was intubated for more than 30 days.

the need for endotracheal intubation was unclear. Of the 4 nonsmokers noted (mean age, 31), only 1 required endotracheal intubation; on the other hand, of the 5 smokers noted (mean age, 38), 4 required mechanical ventilation, and in the 1 patient who did not, the $Paco_2$ reached 71 mm of mercury. A regimen of an antibiotic effective against *M pneumoniae* was begun on an average of 10 days (range, 2 to 16 days) after the onset of symptoms in 17 patients and, similarly, in 19 patients, on an average of the sixth hospital day.

Eight patients received corticosteroid therapy. Of the six male patients who were treated with steroids, three required mechanical ventilation. In one patient, endotracheal intubation was instituted for support during an open lung biopsy, and a brief course of corticosteroids was begun on the fourth hospital day[7]; in the other two patients, corticosteroid therapy was begun late (≥10 days after symptom onset) and only after intubation.[8,14] Open lung biopsies showed a consolidative pneumonitis with bronchiolitis obliterans in one of these patients[8] and a confluent nodular infiltrate with bronchiolitis obliterans in the other.[7] Using a more current classification scheme, the pathologic descriptions of these two cases suggests that they are bronchiolitis obliterans with organizing pneumonia.[65] Although the third intubated male patient received corticosteroids after the development of adult respiratory distress syndrome,[14] clearing of the infiltrate was noted after the administration of steroids. In the other three nonintubated male patients, two received tetracycline and corticosteroids simultaneously, and rapid improvements were noted[46,48]; one of these steroid-responsive patients had a clinical diagnosis of bronchiolitis.[48] In the third patient, prompt recovery from a "moribund" state was noted only after a course of steroids was started.[47] In the two female patients who received steroids, it was evident that steroid administration was salutary, and neither required mechanical ventilation.[46,51]

Open lung biopsies in six patients with nonfatal respiratory failure revealed infiltration of bronchiolar walls with acute and chronic inflammatory cells (cellular bronchiolitis) in two patients,[6,43] bronchiolitis obliterans with organizing pneumonia in three patients,[6-8] and an "active pneumonitis" in one patient.[13] Rollins and co-workers reviewed the open lung biopsies of six patients with *M pneumoniae* pneumonia (2 with nonfatal respiratory failure were mentioned earlier) and noted acute and chronic cellular bronchiolitis in five of them; the sixth patient had bronchiolitis obliterans with organizing pneumonia.[6]

Fatal Respiratory Failure

Among the 13 cases shown in Table 2, the average age was 27 years. A regimen of an antibiotic effective against *M pneumoniae* was begun an average of 15 days after symptom onset (range, 1 to 29 days) and on an average of the eighth hospital day in 7 patients. Two patients received corticosteroids. In one patient, the steroid dosage was unclear, and death was due to multiple pulmonary emboli and *Pseudomonas* species sepsis.[8] The other patient received only one dose of corticosteroid.[17]

Of the 13 patients who died of respiratory failure, 9 (69%) had thromboemboli either strongly suspected or documented; most of these were pulmonary emboli. There were 2 sudden deaths, and autopsies revealed bronchiolitis and purulent bronchiectasis in a 6-year-old boy[9] and bronchiolitis obliterans and pulmonary thrombi in a young man with rheumatic heart disease.[57]

Fatal Cases Without Respiratory Failure

In six of the seven patients in Table 3 for whom data were available, the average age was 45 years. The cause of death included thromboembolism in three patients,[40,62,63] meningoencephalitis in two patients,[55,61] myocarditis in one patient,[64] and "indeterminate" cause in one patient.[60] None of the patients were noted to have received steroids.

TABLE 2.—*Fatal Respiratory Failure*

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication/ Autopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
1.....	3	F	--	CF 1:8→1:64	Erythromycin (23/21)	Hemolytic anemia; DIC, renal failure; candida sepsis; ? thromboembolism	Yes	--	Nilsson et al, 1971[53]
2.....	6	M	--	CF 1:1,024; CA 1:512	Erythromycin (29/12)	Bronchiolitis; bronchiectasis	Yes	Pco_2 125; Po_2 158 (100%)	Halal et al, 1977[9]
3.....	8	F	Silent atrial septal defect	"Serologic evidence"	Erythromycin (?/?)	Stevens-Johnson syndrome; obliterative bronchitis; pericarditis	Unclear	--	Edwards et al, 1983[54]
4.....	13	M	--	CF 1:10,000; CA 1:128	No appropriate antibiotics	Multiple thrombi in leptomeninges; bilateral pneumonia	Unclear	--	Dorff and Lind, 1976[55]
5.....	20	M	--	CF 1:8→1:64; pos DNA probe	Erythromycin (10/1)	DIC/ARDS; open lung: pulmonary thrombosis, diffuse alveolar damage	Yes	--	Donat, 1992[56]
6.....	23	M	Rheumatic heart disease	CF 1:32 → > 1:256; CA 1:40 → 1:160	Erythromycin (17/10)	CHF, sudden death; interstitial pneumonitis; BO, PE	Yes	--	Benisch et al, 1972[57]
7.....	28	F	Nonsmoker, pregnant	CF 1:2,048; CA 1:4 → 1:16	Erythromycin/ steroids (?/?)	Multiple PE; pseudomonas pneumonia/sepsis	Yes	Po_2 52 (28%)	Fraley et al, 1979[8]
8.....	30	F	--	Postmortem tissue culture	No appropriate antibiotics	Shock, PE; DIC	Yes	--	Koletsky and Weinstein, 1980[15]
9.....	31	F	Postpartum	CF 1:4 → 1:128	Doxycycline (6/1); 1 dose of steroid	Interstitial fibrosis	Yes	Pco_2 90	Kaufman et al, 1980[17]
10.....	31	M	--	CF 1:4 → 1:64	Erythromycin (1/1)	CHF; PE	Yes	--	Sands and Rosenthal, 1982[58]
11.....	37	M	Diabetes mellitus; cirrhosis	CF 0 → 1:256	No appropriate antibiotics	DIC, shock, myocarditis; hemorrhagic pneumonia	Yes	--	DeVos et al, 1974[59]
12.....	55	F	--	CF < 1:8 →1:32	No appropriate antibiotics	Interstitial pneumonitis; left main pulmonary artery embolus	Unclear	--	Meyers and Hirschman, 1972[60]
13.....	68	F	--	CF 1:10→1:320	Tetracycline (18/7)	Pancreatitis/diabetes; PE, DIC	Yes	--	Mardh and Ursing, 1974[52]

ARDS = adult respiratory distress syndrome, BO = bronchiolitis obliterans, CA = cold agglutinin (immunoglobulin M), CF = complement fixation (immunoglobulin G), CHF = congestive heart failure, DIC = disseminated intravascular coagulation, Fio_2 = fractional concentration of supplemental oxygen, PE = pulmonary thromboembolism, pos = positive

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy started.

Discussion

Nearly 50 years ago, a filterable agent was described from the sputum of patients with atypical, cold-agglutinin–positive pneumonia, and the pneumonia was duplicated in laboratory animals.[66] In 1962 Eaton's agent, subsequently characterized as *M pneumoniae*, was grown on agar.[67] It is one of the smallest free-living organisms known, and it lacks the cell wall of most bacteria.

According to epidemiologic studies regarding this agent, *M pneumoniae* infections are common. Most of the illnesses are mild, and the patients are never seen by practitioners. It is estimated that *M pneumoniae* accounts for as many as 20% of all cases of community-acquired pneumonia in the general population and for as many as 50% in closed populations such as students and military recruits living in dormitories.[3] In a community survey performed in Seattle, Washington, spanning 11 years, it was determined that *M pneumoniae* accounted for 30% to 60% of all cases of pneumonia in the 5- to 20-year age group.[68] In the subgroup of 15- to 19-year-olds, it was the most common cause of pneumonia.

Unfortunately, the diagnosis of *M pneumoniae* pneumonia is often delayed and retrospective because of the

lack of a rapid, accurate, and widely available diagnostic test. More specialized tests, such as culture, detecting antigen in sputum by the use of indirect immunofluorescence with monoclonal antibodies and enzyme-linked immunoassay, complementary DNA probes for ribosomal RNA detection, and polymerase chain reaction for detecting DNA are done only in specialized laboratories.[69] Diagnostic testing is also complicated by the fact that a prolonged nasopharyngeal carriage for *M pneumoniae* may exist even after successful treatment with antibiotics[70] and may account for relapses.[71]

A bias for the most critically ill patients to be seen at referral centers[30] or possible differences in virulence between strains[45] may account for the higher rate of fulminant cases reported by some authors. Such reasoning, however, would not likely explain the greater incidence of severe cases reported in young healthy adults, as many are single case reports. Because *M pneumoniae* pneumonia is endemic, with epidemics occurring every two to six years,[4] the disparity in the number of severe cases collected by different workers may reflect this cycle. The possibility that such epidemics account for the greater incidence in young men due to the greater clustering of young men in organizations such as the military can only be conjectured. Although it has been suggested that a correlation exists between severe respiratory involvement and high cold-agglutinin titers,[8] a perusal of our list does not support this observation.

Surprisingly, in the studies of community-acquired pneumonia examined, the mortality rate for patients admitted to a hospital with *M pneumoniae* pneumonia (3% to 5%) is lower than that for all etiologic agents combined (mean, 12%). The frequency with which mycoplasmal infection results in respiratory failure or death is therefore probably low, but given the high estimated incidence of *M pneumoniae* infections, sporadic cases are not unusual. Most fulminant cases are essentially documented as case reports, of which we found only 46 to be evaluable.

Nonfatal Respiratory Failure

In the group of 26 patients listed in Table 1, most had no underlying disease and were previously healthy. In light of this, it is ironic that two groups reported "unusually severe" cases of *M pneumoniae* infections in immunocompromised hosts and yet none of these patients had respiratory failure or death.[25,26] In one such report,[25] "severe" infections occurred in four teenagers with immunodeficiency syndromes in whom there were minimal or no changes on chest radiographs and in whom rapid improvement occurred with antibiotic therapy. In the other report, "severe" *M pneumoniae* pneumonia was described in five children with sickle cell anemia, all of whom had uneventful recoveries.[26]

Most of the reported patients were young adults. Whether this is due to a lower suspicion for *M pneumoniae* pneumonia in elderly patients with chronic disease

TABLE 3.—*Fatal Nonrespiratory Failure*

Patient	*Age, yr*	*Sex*	*Underlying Disease or Risk Factor*	*Diagnostic Tests*	*Antibiotics*†*	*Complication or Cause of Death*	*Source*
1	Unknown	Unknown	Unknown	Unknown	Unknown	PE	White et al, 1981[40]
2	17	M	- -	CF 1:1,000; CA 1:256	Antibiotics (?/?)	Bilateral pneumonia; meningoencephalitis; brain edema	Dorff and Lind, 1976[55]
3	29	M	- -	CF 1:32 → 1:256	Erythromycin (15/10)	Cerebritis, meningitis; cerebrovascular thrombi	Weinblatt and Caplan, 1980[61]
4	39	F	- -	CF 1:64 → 1:128	Tetracycline and erythromycin (7/3)	Pleural effusion; "indeterminable cause of death"	Meyers and Hirschman, 1972[60]
5	45	M	- -	Pos throat culture; CA 1:64	Tetracycline (7/1)	Psychosis; bilateral PE/ infarctions	Sterne and, Biberfeld, 1969[62]
6	70	F	- -	Pos postmortem tissue culture	Tetracycline (8/?)	Diffuse thrombo-emboli; hemolytic anemia; interstitial pneumonitis; bronchiolitis, bronchitis	Maisel et al, 1967[63]
7	71	M	- -	Pos blood/peri-cardial fluid culture	Antibiotics (?/?)	Myocarditis; pleuritis; minimal consolidation	Naftalin et al, 1974[64]

CA = cold agglutinin (immunoglobulin MG), CF = complement fixation (immunoglobulin MG), PE = pulmonary thromboembolism, pos = positive

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy begun.

or a greater prevalence and severity of the disease in younger persons is unknown. There were nearly three times as many male as female patients in the sample analyzed.

It is premature to comment on the use of tobacco and the need for mechanical ventilation in this series despite the suggestive association, because only nine patients had their smoking status documented. Nevertheless, smokers have a substantial increase in neutrophils in their lungs,[72] and these cells may play a crucial role, by the release of proteolytic enzymes or oxidants, in the pathogenesis of lung injury caused by this disorder. Similarly, it is inappropriate to construe that the untimely administration of antibiotics was associated with adverse outcomes. In many instances, however, antibiotic therapy was delayed and often started after agents ineffective against *M pneumoniae*, such as a β-lactam, were tried. We support the observation made recently that it is clinically difficult to predict the etiologic agent of a community-acquired pneumonia[31] and that empiric antibiotic therapy should initially include coverage for both "typical" (such as *Streptococcus pneumoniae*) and "atypical" (such as *M pneumoniae*) organisms. The fulminant cases of *M pneumoniae* pneumonia we have reviewed emphasize the point that classifying a case of pneumonia as either a typical or atypical form, based on the abruptness of onset, severity of symptoms, and purulence of sputum, is an unreliable method on which to base empiric antibiotic therapy. Moreover, we stress that empiric monotherapy with the newer cephalosporins or penicillins for community-acquired pneumonia, increasingly popular in the United States,[31] has no scientific basis because these agents are not effective against *M pneumoniae*, *Legionella pneumophila*, or *Chlamydia pneumoniae*. Similarly, the fluoroquinolones are being increasingly used to treat bronchitis and community-acquired pneumonia, but their efficacy against *S pneumoniae* is doubtful.

Immune mechanisms may be important in the pathogenesis of *M pneumoniae* pneumonia. Active *M pneumoniae* infection has been shown to transiently depress cell-mediated immunity, as demonstrated by a decrease in skin and lymphocyte stimulation responses to purified-protein derivative of tuberculin.[73] On the other hand, protein antigens on the cell surface of *M pneumoniae* have been shown to induce cellular immunity, as confirmed by both lymphocyte transformation in vitro and enhancement of delayed cutaneous hypersensitivity.[74] Noriega and co-workers suggested that a host-cellular immune response to *M pneumoniae* played a central role in the severe pneumonitis that occurred in a patient.[47] The proposed hypothesis was that previously sensitized lymphocytes from an earlier infection are activated during a subsequent infection and release supranormal levels of "mediators" that cause local tissue destruction and precipitate a cascading inflammatory response. This postulate was supported by later investigators in a case report[51] and by a laboratory experiment in which hamsters pretreated with antithymocyte globulin, which decreases the number of lymphocytes, showed less severe pneumonia than control animals.[75] These studies suggest that indeed an excessive host-cellular response to the organism may be responsible for the lung injury.

Clinical studies also corroborate a role for the cellular immune system in the pathogenesis of *M pneumoniae* pneumonia. It has been suggested that a lack of an immune response accounted for the absence of pneumonic infiltrates in four children with immunodeficiency syndromes.[25] Perez and Leigh commented on the underwhelming incidence of *M pneumoniae* infection in children with cancer.[76] In a review of the immunology of *M pneumoniae* infection, it was noted that there was no convincing evidence that cell-mediated immunity played a direct role in resistance to *M pneumoniae* respiratory infections, but experiments showed that hamsters challenged intranasally with *M pneumoniae* had T cells accumulate in the peribronchiolar and perivascular spaces of their lungs with a secondary outpouring of phagocytic cells into their bronchial lumina.[77] The time required for such a host response to develop may be the basis for one author's observation that respiratory failure in his patients developed 7 to 14 days after the onset of their illnesses.[29] The fact that severe *M pneumoniae* pneumonia is not seen with increased frequency in patients with the acquired immunodeficiency syndrome also lends credence to a cellular immunologic basis in the pathogenesis of fulminant cases,[70] although this has not been systematically evaluated.

In contrast to the deleterious role that the cellular immune response may have in patients with *M pneumoniae* pneumonia, local humoral immunity may have an important role in the resistance to mycoplasmal respiratory infections.[77] There is evidence that immunoglobulin levels in respiratory secretions correlate better with resistance to such infections than do circulating antibody levels.[73] Enhanced antibody response in the bronchial lumen may inhibit *M pneumoniae* attachment to the respiratory epithelium and may also, by opsonization, increase phagocytosis of the organism by mononuclear cells. Immunization with the Pi surface protein, the specialized surface structure of *M pneumoniae* that serves as the attachment site to host cells, may also confer protective local humoral immunity.[73]

The stimulation of autoimmune antibodies by *M pneumoniae* antigens cross-reactive with host tissue has been proposed as an explanation for the extrapulmonary manifestations of *M pneumoniae* infections.[78] Except for hemolytic anemia where nonspecific immunoglobulin M interacts with the I antigen of erythrocytes, direct evidence of antibody-mediated injury is lacking.[79] Similarly, there is no evidence that autoantibodies are involved in the lung injury. Although it has been shown that circulating immune complexes are increased in patients with *M pneumoniae* pneumonia and that high levels correlate with the severity of the pneumonia, it is unclear whether they have a pathogenic role or are the result of the disease.[80]

Pathologic support for a cellular immunologic response in *M pneumoniae* pneumonia comes from Rollins

and co-workers in their description of a lymphoplasmacytic bronchiolar wall infiltrate with a neutrophil-rich intraluminal exudate[6]—that is, a cellular bronchiolitis. They emphasized that *M pneumoniae* is often omitted from the differential diagnosis even when this characteristic bronchiolitis is seen on lung biopsy specimens, but underscored that this pathologic appearance may be seen with viral, other bacterial, and allergic disorders as well. A case of bronchiolitis obliterans with organizing pneumonia from an open lung biopsy was also described by these authors.[6] Typically in these cases, polypoid masses of granulation tissue are found filling the respiratory bronchioles and alveolar ducts with a lymphoplasmacytic infiltration of the adjacent alveolar interstices.[65] Unfortunately, interpreting much of the pathologic literature regarding *M pneumoniae* pneumonia is difficult because the classification and nomenclature of bronchiolitis, which is increasingly described in various lung diseases, are rapidly evolving.[65]

Of the six nonfatal, fulminant cases of pneumonia we found reported in which lung biopsies were done, two had a cellular bronchiolitis[6,43] and three others had pathologic descriptions that are consistent with bronchiolitis obliterans with organizing pneumonia.[6-8] Cellular bronchiolitis is usually self-limiting, but a chronic cough may persist and require the use of corticosteroids for resolution.[65] In the eight patients with nonfatal respiratory failure who received corticosteroids, six were specifically noted to have responded favorably to steroid therapy.[14,46-48,51] Given the frequent recognition of bronchiolitis and bronchiolitis obliterans with and without organizing pneumonitis in this series of patients, one must question whether steroid responsiveness relates to the presence and extent of these pathologic lesions. Bronchiolitis was diagnosed in a patient with severe obstructive and ventilatory defects who, despite considerable hypoxemia and hypercarbia, responded well to steroids and avoided mechanical ventilation.[48]

In contrast to the mild course of bronchiolitis, postinfectious bronchiolitis obliterans may have a malignant and fatal course with irreversible and extensive scarring of the bronchioles. The early use of corticosteroids is considered the treatment of choice.[65] Two of the three patients with bronchiolitis obliterans with organizing pneumonia due to *M pneumoniae* were smokers, and both required mechanical ventilation despite steroid administration.[7,8] Either late[8] or brief[7] administration of steroids is a plausible explanation for its ineffectiveness. In the third patient with bronchiolitis obliterans with organizing pneumonia,[6] smoking status and steroid usage were unclear. It is interesting that in patients in whom bronchiolitis obliterans with organizing pneumonia develops in the setting of chronic graft-versus-host disease after allogeneic bone marrow transplantation, there is a similar lymphoplasmacytic infiltration of the bronchioles, and early treatment with high-dose corticosteroids has been emphasized to resolve the lung disease.[81] The early administration of corticosteroids was recommended to stave off fibroblast proliferation in severe cases of *M pneumoniae* pneumonia that do not show improvement after a few days from symptom onset.[17] Pulmonary fibrosis developed in a patient with a well-documented case of *M pneumoniae* pneumonia and who responded dramatically to a course of corticosteroids a year after her initial pneumonia.[16] Additional cases of *M pneumoniae* pneumonia were reported in which fulminant evolution into diffuse interstitial fibrosis occurred.[82] Whether these patients had a component of bronchiolitis obliterans with organizing pneumonia or bronchiolitis obliterans early in the clinical course is unclear.

Fatal Cases

The incidence of fatal *M pneumoniae* pneumonia is low, especially in outpatient series. The relatively young age of the fatal cases in the cases summarized in Tables 2 and 3 (mean, 33 years) is intriguing in light of the fact that age is often regarded as an independent risk factor for increased morbidity and mortality in pneumonia.[83] In a five-year prospective study of community-acquired pneumonia, an overall mortality rate for all etiologic agents of 8.5% was documented for those younger than 60 years and 28.6% for those 60 and older.[41] As previously noted, whether this increase in the severity of *M pneumoniae* pneumonia in younger and presumably more immunocompetent hosts is a true risk and due to host factors or whether the collecting of cases is biased because of greater prevalence or greater awareness in younger patients is unresolved.

In an earlier review of 11 fatal cases of *M pneumoniae*, it was noted that vascular thromboses with associated infarctions occurred in nearly half of the patients.[15] In our more current review of 20 fatal cases, thromboembolism was a salient feature and was either suspected (1 case) or documented (12 cases) in 65% of the patients. In the latter 12 cases, pulmonary embolism was diagnosed in 10 and was either the direct cause[40,57,60,62] or a facilitator of death. The unanswered question is whether the thromboemboli are provoked by the *M pneumoniae* or whether they are the result of venous stasis in very ill patients. It has been suggested that a cold agglutinin-induced hemolysis precipitated a hypercoagulable state in a patient, leading to widespread thromboembolism.[63] Although disseminated intravascular coagulation has been associated with both fatal and nonfatal cases of *M pneumoniae* infection, cases of pulmonary emboli have occurred in the absence of this complication.[40,57,60,62] It is unclear to us why there were no cases of pulmonary emboli noted in the patients with nonfatal respiratory failure. Because most of the fatal cases with thromboembolism were diagnosed at autopsies, a possible explanation for this discrepancy is that nonfatal thromboembolism also occurred, but was simply not suspected in some of those patients who recovered.

Summary

This review of fulminant *Mycoplasma pneumoniae* infections confirms the widely held belief that the etiologic diagnosis of community-acquired pneumonia is

frequently putative and treatment empirical. It also emphasizes that empiric therapy based on the conventional scheme for dividing community-acquired pneumonia into typical and atypical forms is deceptive and unreliable. Because of the high frequency of infections with *M pneumoniae*, severe cases of *M pneumoniae* pneumonia are not rare, but are probably underdiagnosed owing to unawareness or to an underestimation of such cases and to the lack of a rapid method to diagnose *M pneumoniae*. Because of host factors or on epidemiologic grounds, fulminant cases seem to be more common in young healthy adults, in males, and possibly in smokers. Enhanced host-cellular immune response and cytokine elaboration, increasingly implicated in the pathogenesis of various diseases, may be involved in fulminant cases of *M pneumoniae* pneumonia as well. Rarely, fatal cases may show little or no pulmonary involvement. Because of the high frequency with which inflammatory injury to the bronchioles is observed, empiric corticosteroid therapy should be considered in cases of respiratory failure. Prophylaxis against and investigation for thromboembolism should be strongly considered in life-threatening cases.

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Obstructive Sleep Apnea
Trends in Therapy

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The National Commission on Sleep Disorders Research, in its report to Congress, concluded that the primary care community generally does not understand sleep disorders. Obstructive sleep apnea carries a risk of substantial morbidity and mortality. Excessive daytime sleepiness results from fragmented sleep and microarousals associated with apneic events. It causes poor work performance and increases the incidence of automobile accidents due to driving while drowsy. The commission estimates that the loss of productivity in the United States from excessive daytime sleepiness is more than $20 billion per year. Obstructive sleep apnea is strongly associated with hypertension, myocardial infarction, and stroke. Risk factors for obstructive sleep apnea include male sex, obesity, older age, craniofacial anomalies, and familial risk. Treatment is based on documenting the disorder by polysomnography. Medical management of the syndrome includes weight loss and nasal continuous positive airway pressure. A network of follow-up and support is necessary to maintain compliance. Surgical treatment is reserved for those for whom nasal airway pressure treatment fails. A surgical protocol is presented that demonstrates efficacy equal to nasal airway pressure treatment. Primary care physicians should assume the responsibility of identifying patients at risk for obstructive sleep apnea and refer them appropriately.

(Riley RW, Powell NB, Guilleminault C, Clerk A, Troell R: Obstructive sleep apnea—Trends in therapy. West J Med 1995; 162:143-148)

Obstructive sleep apnea syndrome (OSAS) continues to be little more than a medical curiosity to primary care physicians. Thought to be of little importance, the hallmark symptom of snoring is more a subject of humor than of serious scientific investigation. In 1988 the United States Congress established the National Commission on Sleep Disorders Research "to conduct a comprehensive study of sleep disorders and to develop a long-range plan for the use and organization of national resources to deal effectively with sleep disorders research and medicine."[1(p4)] The commission found that the primary care community generally did not understand sleep disorders. In one survey, the commission conducted searches of computerized clinical databases in 50 primary care settings throughout the United States, accumulating data on more than 10 million patients. Even though ICD-9 [*International Classification of Diseases*, 9th revision] codes for sleep disorders have been part of the international classification system for nearly 20 years, only 73 specific cases of sleep disorders were identified in this sample. Considering currently accepted prevalence estimates, more than a million cases should have been seen. To further confirm these results, the raw records of more than 10,000 patients in primary care clinics were carefully examined by commission investigators. Every physician-patient interaction from a patient's first visit to the time of the study was examined, adding up to more than 50,000 physician-patient interactions. In this huge mass of data, not a single appropriate response to a patient with a sleep-related complaint was found.

The most serious sleep disorder in terms of morbidity and mortality is OSAS, which represents greater than 80% of the diagnoses made by the Stanford (California) Sleep Disorders Center.[2]* The syndrome is characterized by recurrent episodes of obstructed breathing during sleep, caused by the collapse of the upper airway. The trachea and bronchi maintain patency by cartilaginous support. Upper airway patency is critically dependent on the dilator muscles of the pharynx. Sleep results in the loss of tone of the upper airway muscles and, specifically, the dilator muscles. Patients with "disproportionate" anatomy of the upper airways are therefore susceptible

*See also the editorial by A. E. Sher, MD, "Treating Obstructive Sleep Apnea Syndrome—A Complex Task," on pages 170-172 of this issue.

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ABBREVIATIONS USED IN TEXT

CPAP = continuous positive airway pressure
NS = not significant
OSAS = obstructive sleep apnea syndrome
RDI = respiratory disturbance index
SaO_2 = arterial oxygen saturation
SD = standard deviation

to complete airway collapse during sleep. This is usually preceded by many years of loud, heroic snoring that is the result of muscle relaxation and partial airway obstruction. With complete obstruction, snoring is interrupted by periods of silence lasting ten seconds to more than a minute. The apneic periods are characterized by paradoxical respiratory efforts and often severe arterial hypoxemia. The apneic periods are terminated by sleep reversals or microarousals that produce increased muscle tone and airway patency, which correspond to a generalized startle response or gasping that is usually noted by a spouse. After a brief period of normal breathing, this cycle of events is repeated. This sequence of events can occur several hundred times during a normal night of sleep.

The primary symptom of obstructive sleep apnea is excessive daytime sleepiness or hypersomnolence due to the fragmented sleep and microarousals associated with the apneic events.[3] Excessive daytime sleepiness may result in impaired cognition and memory loss that in turn can result in poor performance at work and emotional disturbance. A major concern with excessive daytime sleepiness is driving while drowsy, which increases the risk of automobile and truck accidents. The risk of such accidents has been reported to be as much as seven times greater in patients with OSAS than in the general population.[4] The national commission estimates the loss of productivity in the United States from daytime hypersomnolence to be greater than $20 billion per year.

In addition to the effects of excessive daytime sleepiness on productivity, several studies have demonstrated strong associations between snoring and hypertension, myocardial infarction, and stroke.[5,6] One study determined existing morbidity and incident mortality over a seven-year period among patients with sleep apnea who had had tracheotomies and been conservatively treated (for example, weight loss).[7] Compared with the general population, patients with sleep apnea have twice the prevalence of hypertension, three times as much coronary artery disease, and four times as much cerebrovascular disease. A recent case-control study from Italy found that the risk of myocardial infarction was about four times higher in patients who reported snoring every night than in those without this history.[8] Patients who undergo treatment of their obstructive sleep apnea show improvement in their morbidity-mortality risks.

Prevalence estimates have shown some discrepancy because of the diversity of study groups and sizes. Employed men in Israel had a 5% incidence of OSAS,[9] whereas employed men in Germany aged 19 to 61 had a 10% incidence of the syndrome.[10] Both of these studies involved relatively small groups (< 100). In contrast, a recent study examined sleep studies from more than 600 patients in a population-based sampling of working men and women aged 30 to 60 years. In all, 9% of women and 24% of men showed OSAS above the minimum cutoff level, and 4% of women and 9% of men in this age group have substantial OSAS that could increase cardiovascular risk and produce debilitating daytime hypersomnolence.[11]

The risk factors for OSAS include male sex, obesity, older age, craniofacial anomalies, and familial risks.[12] About 85% of patients diagnosed with the syndrome are male. The male sex predisposition to a greater number of obstructive respiratory events has been noted even among "healthy" volunteers. Preliminary data from the study of such patients between the ages of 7 and 75 years in Cleveland suggest that men are six times more likely than women to have the syndrome.[13]

Sleep apnea is most commonly diagnosed in persons between the fifth and seventh decades of life. Symptoms of loud snoring and hypersomnolence may precede the diagnosis by many years. It is not uncommon, however, for symptoms to develop as early as the first or second decade of life. This suggests that mechanisms that lead to the development of sleep apnea may operate over many years. Studies of the general population have shown a clear age-related increase in the number of respiratory pauses during sleep.[14]

About two thirds of the patients with OSAS diagnosed at the Stanford Sleep Disorders Center are obese (>20% ideal body weight). Obesity has been found to be the strongest predictor of OSAS. In one study of elderly patients, obesity was estimated to be about fourfold stronger than the influence of age and twice as strong as the influence of sex in predicting the presence of OSAS.[13]

Several families have been described that have multiple members with sleep apnea. The transmission of OSAS in families is unclear, although the occurrence of the disorder in nonobese male and female family members suggests the importance of genetic factors.[15] Included in the genetic predisposition to OSAS are craniofacial anomalies. Anomalies associated with mandibular maldevelopment (for example, the Pierre Robin syndrome or the Treacher Collins syndrome [mandibulofacial dysostosis]) often lead to OSAS. Preliminary data from an ongoing genetic-epidemiologic study suggest that subjects with a family member with OSAS are 1.5 times more likely to have the disorder.[16]

Diagnosis

Given the high prevalence of symptomatic OSAS in the general population, its serious consequences, and the fact that it is readily treatable, primary care physicians have the responsibility to identify patients at risk for the disorder and to make appropriate referrals. Clinical

features that are helpful in identifying such patients include habitual snoring, nocturnal gasping, episodes of apnea, and daytime somnolence.[17] Any combination of these symptoms is strongly indicative of substantial obstructive sleep apnea. As previously stated, most patients with this syndrome are obese. When seen in combination with habitual snoring, obesity becomes a significant risk factor for the disorder in men, though this is less the case in women.[11]

Polysomnography is the primary method of determining the presence of OSAS. This procedure is usually done in a sleep laboratory; more recently, however, ambulatory monitoring has also become available. The polysomnogram systematically monitors the electroencephalogram, electro-oculogram, chin and leg electromyograms, electrocardiogram (modified V_2 lead), air flow, thoracic and abdominal efforts, and pulse oximetry. The measurements with the greatest clinical importance are the respiratory disturbance index (RDI), which is the number of respiratory events per hour of sleep, and oximetry. Respiratory events include apneas, which are defined as the cessation of breathing for greater than ten seconds, and hypopneas, which are defined as a decrease in tidal volume by at least 50% from baseline. The RDI represents the total number of apneic and hypopneic episodes per hour of sleep (RDI = apnea + hypopnea ÷ total sleep time × 60). An RDI of more than 5 is considered the upper limits of normal. An RDI of 20 or higher is considered substantial enough to produce daytime hypersomnolence and increased cardiovascular risk, although patients with an RDI of less than 20 can also experience microarousals and daytime hypersomnolence requiring treatment. Another important measurement is the oxygen desaturation level (Sa_{O_2}), which is the lowest blood oxygen level observed in a recording period. An Sa_{O_2} of less than 85% is relevant.

Treatment

Medical Management

We have reviewed the positive correlation between obesity and obstructive sleep apnea. It would therefore follow that weight loss would be an important consideration in the management of OSAS. In fact, several studies have documented that weight loss will, indeed, improve sleep-disordered breathing.[18] In a review of 415 patients at the Stanford Sleep Disorders Center who underwent surgical correction of their problem, almost all the patients lost a considerable amount of weight postoperatively (7 to 18 kg [15 to 40 lb]). Despite aggressive dietary counseling and reinforcement, essentially all patients had regained their weight to their preoperative level after 6 to 12 months. Although it remains an integral part of treatment, weight loss as the sole or even primary treatment modality for OSAS is inadequate.

Nasal continuous positive airway pressure (CPAP) is the primary form of treatment of OSAS. More than 85% of the patients seen at the Stanford Sleep Disorders Center are treated by this method. Nasal CPAP was originally described in 1982.[19] The concept is to deliver positive pressure through a nasal mask to the pharynx, thereby creating a pneumatic stent. Excessive daytime sleepiness is reversed, and the cardiopulmonary sequelae are eliminated with nasal CPAP.[20] One problem with nasal CPAP, however, is the issue of long-term patient compliance. In one study, long-term home nasal CPAP therapy was analyzed, and a compliance rate of 75% was found.[21] This finding was later reconfirmed.[22] These reports had inherent flaws because compliance was based on subjective patient reporting. In a recent review, objective data of nasal CPAP compliance were obtained by placing covert monitors on the nasal CPAP machines of a select group.[23] The results indicate that self-reporting of estimated CPAP use during the night and over a long period of time is exaggerated. In fact, objective data suggest that nasal CPAP compliance is less than 50%. At the Stanford Sleep Disorders Center, nasal CPAP continues to be the primary modality because the clinic provides a network of follow-up and support to maintain an acceptable level of compliance. A follow-up report further demonstrated that limited or part-time use of CPAP is not a satisfactory method of controlling obstructive sleep apnea.[24]

Surgical Management

Surgical treatment of obstructive sleep apnea is limited to about 15% of the patients seen at the Stanford Sleep Disorders Center. It is usually reserved for those persons in whom a trial of nasal CPAP fails. The most common problems cited are nasal irritation, rhinorrhea, claustrophobia, and inconvenience.

The first surgical procedure for the treatment of obstructive sleep apnea was a tracheostomy, which conceptually bypassed the upper airway obstruction.[25] It was initially described in 1969 and was the treatment of choice during the 1970s. The procedure is now rarely done at Stanford, partly because it is poorly tolerated and there are other surgical procedures that better correct the problem.

In 1979 the initial use of uvulopalatopharyngoplasty as a primary treatment of OSAS was reported.[26] This procedure removes redundant tissue from the palate and tonsil area. It was the treatment of choice in the early 1980s and proved to be an excellent method of controlling snoring; however, several retrospective reviews reported improvement in only 50% of the patients and complete control of the syndrome in only about 30%.[27,28] This relative lack of success has led to misunderstanding and confusion about the surgical treatment of obstructive sleep apnea.

The Stanford surgical group subsequently reviewed cases in which uvulopalatopharyngoplasties were unsuccessful and concluded that although the procedure eliminated the obstruction at the level of the soft palate, persistent obstruction was present at the base of the tongue.[29] It is now generally accepted that there are many sites in the upper airway, including the soft palate,

pharyngeal walls, and base of tongue, that possibly contribute to obstruction. Based on this concept of the potential for multiple obstructive sites, a Stanford surgical protocol was designed in 1988.[30] These surgical procedures represent a modification of techniques previously reported in the maxillofacial and reconstructive surgical literature.[31] The protocol represents improved surgical treatment of the disorder and offers an alternative to patients intolerant of nasal CPAP.

Surgical Protocol

The surgical protocol begins with a polysomnogram and presurgical evaluation, including physical examination, cephalometric roentgenograms, and fiberoptic pharyngoscopy. The goal of this evaluation is to determine the site or sites of obstruction and then to direct treatment to the appropriate areas. The physical examination emphasizes evaluation of the head and neck. It includes a close examination of the nasal cavity to identify obstructing deformities of the septum and turbinates; oropharyngeal obstruction from a long, redundant soft palate or hypertrophic tonsils; and hypopharyngeal obstruction from a prominent base of tongue. The fiberoptic pharyngoscopy, which is positioned transnasally, allows close examination of the oropharyngeal and hypopharyngeal areas and supplements the physical examination. Particular attention is given to the area of the soft palate and the base of the tongue, using the modified Mueller technique.[32]

Cephalometric analysis is used to confirm the findings of the physical and fiberoptic examinations. Figure 1 shows a cephalometric tracing and its anatomic landmarks. The techniques and norms have been described previously.[33] The usefulness of the cephalometric analysis has been confirmed elsewhere.[34] The presurgical evaluation allows for a classification according to the site of obstruction: type 1, oropharynx; type 2, oropharynx/hypopharynx; and type 3, hypopharynx. Patients are considered to have oropharyngeal obstruction when a redundant soft palate or hypertrophic tonsils are noted on the physical examination, the soft palate collapses against the posterior pharyngeal wall with the modified Mueller maneuver on fiberoptic examination, and the cephalometric analysis shows a long, soft palate. Hypopharyngeal obstruction is considered to be present when the base of the tongue collapses against the posterior pharyngeal wall and restricts visualization of the larynx on the physical and fiberoptic examinations, or the cephalometric analysis demonstrates a narrow posterior airway space. Patients with OSAS who have mandibular skeletal deficiency documented by cephalometric analysis (sella-nasion B point < 76 degrees) almost uniformly have a narrow posterior airway space and base of tongue obstruction.

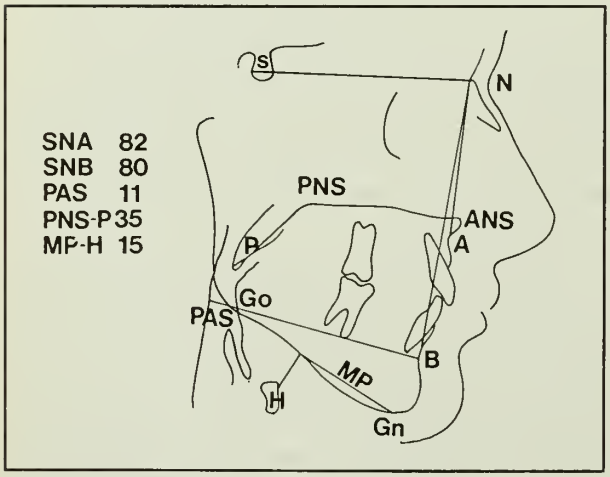

Figure 1.—A cephalometric tracing is shown. The numbers represent a normal tracing and measurements. **A** = subspinale (deepest point of maxilla), **ANS** = anterior nasal spine, **B** = supramentale (deepest point of mandible), **Gn** = gnathion (inferior point of chin), **Go** = gonion (angle of mandible), **H** = hyoid bone, **MP** = mandibular plane (line Go to Gn), **MP-H** = distance (mm) of mandibular plane to hyoid, **N** = nasion, **P** = palate (tip), **PAS** = distance (mm) of tongue base to posterior pharyngeal wall, **PNS** = posterior nasal spine, **PNS-P** = distance (mm) of posterior nasal spine to palate, **s** = sella turcica, **SNA** = angle (degrees) of sella nasion point A, **SNB** = angle (degrees) of sella nasion point B

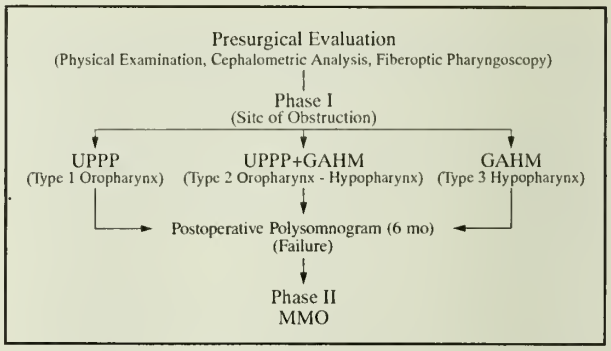

Figure 2.—The diagram is of the Stanford Sleep Disorders Center surgical protocol for the treatment of the obstructive sleep apnea syndrome. **GAHM** = genioglossus advancement with hyoid myotomy, **MMO** = maxillary and mandibular advancement osteotomy, **UPPP** = uvulopalatopharyngoplasty

Once the diagnosis of OSAS has been made by polygraphic monitoring and the sites of obstruction are identified, the reconstruction of the upper airway according to the surgical protocol is undertaken (Figure 2). There are possibly two phases to upper airway reconstruction. Phase I therapy is considered a conservative approach. Persons with isolated obstruction at the level of the soft palate receive uvulopalatopharyngoplasty, and patients with obstruction at the base of the tongue undergo a conservative tongue advancement that consists of anterior repositioning of the genioglossus muscle and hyoid bone. If the patient has both palatal and base of tongue obstruction, they receive both procedures. The time required to do the operation is about an hour. The morbidity associated with this procedure is low, and the mean hospital stay is about two days.

Six months after the operation, patients undergo a second polysomnogram to determine surgical success. Success is defined as postoperative polysomnographic

TABLE 1.—*Stanford Sleep Disorders Center Surgical Protocol Results (239 Patients)*

Surgery Groups	Patient Success/ Total Patients No./No.	Success Rate, %
Phase I		
Genioglossus advancement with hyoid myotomy plus uvulopalatopharyngoplasty	133/223	60
Genioglossus advancement with hyoid myotomy	4/6	66
Uvulopalatopharyngoplasty	8/10	80
Total	145/239	61
Phase II		
Maxillary and mandibular osteotomy	24/24	100

findings equivalent to those of the nasal-CPAP study or a postoperative RDI of less than 20 with at least a 50% reduction over the preoperative study and Sao_2 levels equivalent to those seen with nasal CPAP. In addition to objective polygraphic data, patients must also experience improvement in their snoring and sleep hygiene. The elimination of daytime hypersomnolence must correspond to reports of better quality sleep, improved ability to concentrate, elimination of the need for naps, and improved work performance.

Patients with residual sleep apnea will be offered phase II therapy. Phase II therapy consists of maxillary and mandibular advancement osteotomies. The surgical time for phase II is about three hours. Although conceptually this would seem to be an aggressive therapy, the morbidity is low and the mean hospital stay is only 2.4 days.

The results of the surgical protocol are shown in Table 1. In all, 239 patients entered phase I therapy, with most requiring genioglossal advancement with hyoid myotomy plus uvulopalatopharyngoplasty. Treatment was successful for 61% of the patients. The results were based on the six-month polysomnogram and included analysis of changes in sleep architecture and sleep-disordered breathing. The results indicate that successful surgical treatment is as effective as nasal CPAP (Table 2). More than half of the patients were using nasal CPAP, but they elected surgical treatment because nasal CPAP was an unacceptable long-term treatment modality. Despite rejecting nasal CPAP, they were required to continue its use until the postoperative polysomnogram indicated surgical success. The mean pretreatment RDI was 48.3. The nasal CPAP and postoperative mean RDI were 7.2 and 9.5, respectively (P = not significant [NS]). The mean follow-up period was nine months, but 44 patients have had long-term follow-up (1 to 4 years) with polysomnographic recordings. Only two patients have had recurrence of OSAS. Most of the patients who underwent unsuccessful phase I therapy had severe OSAS (mean RDI, 61.9) and morbid obesity (mean body mass index, 32.3 kg/m^2, with normal being < 27.8 kg/m^2).

Patients treated with phase I surgery were further evaluated by comparing the measurements of surgical success with those of OSAS severity (Table 3). Patients with mildly to moderately severe OSAS had the highest frequency of success (70% to 80%). Surgical success declined to 42% when patients had severe OSAS.

Of the 94 patients for whom phase I therapy failed, 24 elected to have phase II treatment. Most of the patients who declined phase II treatment (and were dropped from the surgical protocol) were older, with a mean age of 51.8 years (standard deviation [SD] = 9.8). The mean age of the patients entering phase II treatment was 43.5 years (SD = 11.5). The 24 patients who underwent unsuccessful phase I surgical treatment showed an improvement, however, in their OSAS phase I postoperative polysomnogram. The mean RDI improved from 75.1 to 56.3, and the mean Sao_2 level improved from 64.0% to 71.9%. All the patients who elected to have phase II therapy had a successful outcome (Table 2). The mean RDI improved from 75.1 (SD = 26.7) to 9.6 (SD = 2.9), and the mean Sao_2 levels improved from 64.0% (SD = 15.9) to 86.4% (SD = 7.0). The nasal CPAP mean RDI and mean Sao_2 was 8.2 (SD = 2.9; P = NS) and 87.5% (SD = 6.7; P = NS), respectively.

Conclusion

The National Commission on Sleep Disorders Research reported that each year the lives of millions of

TABLE 2.—*Phase I and Phase II Surgical Results*

Sleep Measurements	Phase I Treatment n = 145: Before Operation, Before Treatment (SD)	Phase I Treatment n = 145: CPAP (SD)	Phase I Treatment n = 145: After Operation, After Treatment (SD)	Phase II Treatment n = 24: Before Operation, Before Treatment (SD)	Phase II Treatment n = 24: CPAP (SD)	Phase II Treatment n = 24: After Operation, After Treatment (SD)
RDI	47.3 (25.8)	7.2 (4.9)	9.5 (9.5)	75.1 (26.7)	8.2 (2.9)	9.6 (2.9)
Lowest Sao_2, %	72.3 (12.9)	86.4 (11.0)	86.6 (4.5)	64.0 (15.9)	87.5 (6.9)	86.7 (7.0)
Total sleep time, minutes	360 (72.0)	363 (67.0)	379 (63.0)	379 (58.0)	376 (69.0)	388 (56.0)
Stages 3-4 sleep, %	4.4 (5.6)	11.1 (10.8)	8.5 (7.7)	2.7 (4.3)	11.0 (13.3)	8.2 (6.7)
REM sleep, %	11.9 (5.8)	18.3 (7.0)	17.7 (5.6)	8.1 (3.1)	21.2 (8.4)	21.5 (6.1)
Body mass index	29.2 (5.2)	-- --	28.8 (4.9)	31.4 (6.5)	-- --	30.9 (6.0)

CPAP = continuous positive airway pressure, RDI = respiratory disturbance index, REM = rapid eye movement, Sao_2 = arterial oxygen saturation, SD = standard deviation

TABLE 3.—*Results of Phase I Stanford Surgical Protocol by Severity of Obstructive Sleep Apnea Syndrome (OSAS)*

OSAS Severity	RDI	Lowest Sao_2, %	Patient Success/ Total Patients, No./No.	Success Rate, %
Mild	<20	>85	20/26	77
Moderate	20-40	>80	45/58	78
Moderate to severe	40-60	>70	36/51	71
Severe	>60	<70	44/104	42

RDI = respiratory disturbance index, Sao_2 = arterial oxygen saturation

Americans are disturbed, disrupted, or destroyed by the consequences of sleep disorders. Obstructive sleep apnea syndrome is easily diagnosed and treated with nasal CPAP. The Stanford surgical protocol puts to rest the controversy surrounding the surgical treatment of OSAS and demonstrates that it is a viable option for persons intolerant of nasal CPAP. Primary care physicians are in a unique position to alter the staggering effects of sleep disorders on the health and welfare of the nation.

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Epitomes

Important Advances in Clinical Medicine

Physical Medicine and Rehabilitation

Murray E. Brandstater, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association, and the summaries were prepared under the direction of Murray E. Brandstater, MD, and the panel.

Female Athlete Triad

Women have been trying to make themselves an equal force in athletics for the past decade. As this trend continues, physicians are caring more often for young women in competitive sports. Few differences exist in the types or even the frequency of injuries incurred by these women compared with men. So why should physicians, as caretakers of women athletes, view them differently than their male counterparts?

A new epidemic that is unique to female athletes is a triad of separate but interrelated disorders observed in adolescent and young adult women athletes. Consisting of disordered eating, amenorrhea, and osteoporosis, this problem is now called the "Female Athlete Triad." The problem is not new. Well-known elite athletes have come forward with their battle with this triad. Little attention has been paid to recognition, treatment, and prevention, however.

Women athletes are under increasing pressure not only to be strong competitors, but also to have the perfect body type and weight for their chosen sport. Both internal and external pressures from coaches, judges, and parents contribute. Any female athlete is at risk for this triad, but women who participate in endurance and performance sports, such as gymnastics, ballet, and long-distance running, where an athlete is judged on appearance or where low body fat is an advantage, are at highest risk for extreme weight-control behaviors. This, in turn, puts the athlete at substantial risk for the associated disorders of amenorrhea and osteoporosis. Each portion of this triad increases morbidity and mortality, but the three together are dangerous.

The concept of "disordered eating" is relatively new yet extremely common among female athletes, with reports that 15% to 62% practice pathogenic weight-control behaviors. A host of abnormal behaviors are reported, ranging from poor nutrition and restrictive eating at one end to the true eating disorders, anorexia nervosa and bulimia, at the extreme. Any of these disordered eating behaviors can be unhealthy, and an athlete need not fit the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* for an eating disorder to be at risk for serious health problems.

The combination of restrictive eating, excessive training, and decreased body weight may all predispose an athlete to amenorrhea. Athletic amenorrhea is a much more complex phenomenon than once thought, with weight loss, the presence or absence of body fat, and emotional and physical stress all playing a role. The endocrine profile of an amenorrheic female athlete shows a long-term estrogen-deficient state similar to that of postmenopausal women. Because estradiol is extremely important to facilitate calcium uptake into bone, amenorrhea and the associated hypoestrogenic state may predispose female athletes to premature osteoporosis. The long-term effects of amenorrhea on future fertility are still unclear. The data suggest that the reproductive effects of athletic amenorrhea are reversible when the problem is treated.

Osteoporosis, the third part of the triad, refers to early bone loss and inadequate bone formation. Previously considered to be a disease of elders, in young amenorrheic women, 2% to 6% of bone mass can be lost per year, with a total loss of as much as 25% of total bone mass. A young athlete in her 20s may end up with the bone mass of a 60-year-old woman. This puts the athlete at a threefold risk for stress fractures. Of further concern is that bones gain mass only during the first three decades of life, with 95% of maximum density reached by age 18. These athletes are actually losing bone at a time in life when they need to be storing bone for the inevitable loss in later years.

To prevent or reduce the incidence of this triad, awareness and early detection are crucial. Preparticipation physical examination is the ideal time to identify athletes who already have or are at risk of the triad developing. Because

female athletes will rarely bring up issues regarding diet or menstrual history, pertinent questions must be asked. It is often difficult to get an adequate history involving these sensitive issues simply by having an athlete answer a questionnaire. If possible, having a station where the athlete talks with a trainer, psychologist, or physician for a few minutes will elicit a more revealing history.

In addition, checking for subtle physical signs may identify an athlete who already has a disordered eating pattern. These athletes are not necessarily abnormally thin. They may have a decreased pulse rate of 40 to 50 beats per minute. Hypotension, hypothermia, lanugo hair, or a history of fainting can be clues to metabolic disturbances. Parotid swelling (chipmunk cheeks), erosion of tooth enamel or a large amount of dental work, and Russell's sign—finger and nail changes on the first and second digits of the dominant hand—are all signs of bulimia.

Rarely is an athlete excluded from participation for disordered eating or amenorrhea. Yet, these carry substantial possible consequences in psychiatric, endocrine, and skeletal well-being. If, as with other problems identified on an examination, athletes at risk for the triad are denied participation until further evaluation and treatment are initiated, the prognosis for recovery will be improved. It is important for physicians to encourage women to participate in sports in a healthy manner and to help eliminate the "win-at-all-costs" mentality.

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Diagnosing Tibial Stress Injuries in Athletes

As many as 10% of all injuries seen in sports medicine clinics are stress fractures. Running is the most common activity causing these injuries, and the tibia is the most frequent site of injury. The term stress fracture is, however, not appropriate for most tibial stress injuries. Most of the injuries traditionally classified as stress fractures show no evidence of a fracture line or break in the continuity of bone, but exhibit various degrees of bone remodeling and stress reaction.

Radiographs are not a sensitive indicator for bony stress injuries. Magnetic resonance imaging (MRI) has been found superior to isotope bone scanning for diagnosing the degree of tibial stress injuries in running athletes. Magnetic resonance imaging with the fat-suppression technique can clearly identify four grades of tibial bony stress injury: periosteal inflammation associated with the shin splint syndrome, followed by progressive marrow edema, first on fat-suppressed T2-weighted images, then T1-weighted images, and ultimately a cortical stress fracture. Additional advantages of the use of MRI include its multiplanar capability, resulting in precise anatomic localization, lack of radiation exposure, and substantially less imaging time than triple-phase bone scan, although it is currently more costly.

Magnetic resonance imaging is recommended for grading tibial stress injuries in runners and other athletes to allow more accurate recommendations for rehabilitation and a return to impact activity. Athletes with a grade 1 stress injury can usually return to running on grass or soft dirt within three weeks and those with a grade 2 injury within six weeks. Those with grade 3 and 4 injuries are typically more symptomatic, with most having pain with daily ambulation. On physical examination, they have focal bone tenderness and increased pain with percussion, either directly over the involved bone or, in severe cases, at a distance from the site of pain. Athletes with a grade 3 injury are often unable to return to impact activity for 9 weeks and those with a grade 4 injury for at least 12 weeks.

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Alcohol Use and Traumatic Brain Injury

Traumatic brain injury and alcohol abuse are overlapping conditions that interact on several levels. Alcohol abuse, before and after injury, and the presence of alcohol in the blood ("positive blood alcohol level") at the time of the brain injury can complicate recovery. For these reasons it is important to screen for alcohol-related problems in patients with brain injuries and to use various motivational techniques described here to encourage survivors to abstain from alcohol for at least a year after injury.

Preexisting alcohol abuse is common among persons with traumatic brain injury, with as many as 58% reporting a history of alcohol abuse or dependence and 25% reporting previous treatment for substance abuse. Alcohol consumption data also suggest that persons with traumatic brain injury are more likely than their peers to have been heavy drinkers. Alcohol use is involved in many traumatic accidents, including those resulting in brain injury. One study showed that 46% of 2,657 trauma patients had a positive blood alcohol level at admission, 36% were

intoxicated (a blood alcohol level ≥ 22 nmol per liter [100 mg per dl]), and 75% of those who were intoxicated also admitted a longer history of alcohol problems. Alcohol intoxication resulted in a greater likelihood of intubation, intracranial pressure monitoring, respiratory distress, and pneumonia. A positive blood alcohol level has also been found to be associated with a longer duration of agitation and coma and a lower cognitive status at discharge. Although alcohol use frequently declines after these incidents, its use or abuse continues for many people and may result in important complications. Because alcohol may lower the seizure threshold, its use after traumatic brain injury is thought to increase the risk of posttraumatic seizures. The acute effects of alcohol intoxication also mimic the types of impairments found in frontal lobe damage, which is one of the most common patterns of traumatic brain injury. Therefore, even moderate alcohol use may magnify the residual effects on balance, reaction time, and complex concentration. This magnification of impairments may underlie the consistent finding that alcohol use is associated with recurrent brain injuries. Finally, there is evidence that returning to drinking slows the process of recovery after brain damage.

The practical value of this information for clinicians has to do with motivating patients to cut down the amount they use or abstain from alcohol for at least the first year after injury. In the early aftermath of traumatic injury, a window of opportunity exists for health care professionals to promote changes in substance use. Many alcohol researchers now acknowledge that we have underestimated the potential for self-change without formal treatment or with only simple advice. In this regard, even brief feedback (especially personally relevant feedback) and specific advice to cut down on alcohol use have been found to be effective in a controlled study of trauma patients. Motivation to change addictive behaviors seems to be enhanced when a clinician adopts a position of nonconfrontation while eliciting the person's own concerns about alcohol use. This nonconfrontational style, called motivational interviewing, has been shown to reduce resistance to alcohol-related treatment. This approach seems especially appropriate for people who are not seeking help for alcohol problems and has been adapted for use in primary care practice.

The basic principles of motivational interviewing applied to patients with traumatic brain injury are as follows: Screen for a history of alcohol problems with measures such as the CAGE (Have you ever felt you ought to **C**ut down on your drinking? Have people **A**nnoyed you by criticizing your drinking? Have you ever felt bad or **G**uilty about your drinking? Have you ever had a drink first thing in the morning [**E**ye opener] to steady your nerves or get rid of a hangover?) or the Short Michigan Alcoholism Screening Test; follow up on positive results in patients with specific questions about alcohol use such as "What kind of drinker are you?" "What kind of effect does alcohol have on you?" "On a typical Monday, how much will you have to drink?" "Over how many hours?" "On a typical Tuesday?" Ask about health, then substance use. Tie comments about substance use to salient health concerns. Inquire about the subjective benefits of using alcohol or drugs, then the costs or adverse effects. Provide information and then ask, "What do you think?" Include information about specific risks related to traumatic brain injury. Provide this information to family or friends when possible. Make specific recommendations, but then leave the decision up to the patient. Ask the patient what is the next step or where he or she wants to go from here, and negotiate some means of checking on the patient's progress toward goals.

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Hemiplegic Shoulder Pain—Early Prevention and Rehabilitation

PREVENTION, EARLY DIAGNOSIS, and treatment of shoulder pain are important to reduce morbidity and, later, to improve the quality of life in patients who have hemiplegic upper extremities after a stroke.

Shoulder pain is a common problem and usually begins early during the course of recovery. The prevalence of shoulder pain in hemiplegic patients has been reported to vary between 16% and 80%. A broad differential diagnosis must be considered. Possible causes include soft tissue lesions such as rotator cuff or capsular tears, adhesive capsulitis, arthritis, fracture, heterotopic ossification, reflex sympathetic dystrophy, thalamic (central) pain, and pain due to cervical radiculopathy or disease in the brachial plexus. At times patients with carpal tunnel syndrome present with a history of shoulder pain. Subluxation of the humeral head does not by itself directly cause pain but may exert traction stress to the periarticular soft tissue with subsequent pain. Patients with neglect have been reported to have a higher incidence of pain in the hemiparetic shoulder.

Preventing shoulder pain should be a goal during the early recovery phase. Positioning of the hemiplegic limb and judicial range-of-motion exercises should be started within 24 hours after a stroke. A sling may be useful in supporting a flaccid arm when the patient is walking. The shoulder should be maintained in an abducted and externally rotated position. When the patient is seated, a forearm trough or a lapboard can be attached to the wheelchair to help prevent subluxation. It is imperative to avoid the downward gravitational pull of the humeral head by properly handling the upper extremity during

therapeutic range-of-motion exercises. Seating positions and prescriptions must be meticulously analyzed to maintain anatomic alignment and to prevent injury to the insensate limb. The overuse of slings may promote contractures. The use of biofeedback and functional electrical stimulation to shoulder-stabilizing muscles has been reported to decrease the incidence of shoulder subluxation and to promote the recovery of function.

If pain develops in a hemiparetic limb, the clinician must make a definitive diagnosis through a careful examination of the upper limbs. Differentiation should be made between soft tissue injury, reflex sympathetic dystrophy, and subluxation. In subluxation there is a palpable gap between the humeral head and acromion. Bicipital and supraspinatus tendinitis can be diagnosed after determining historically important aggravating factors followed by a thorough examination of the painful region. Brachial plexus injury should be considered in a patient who has atypical return of distal function. Electrodiagnostic studies may help to locate the site of lesion.

The early recognition of reflex sympathetic dystrophy and timely intervention are important to reduce morbidity. Reflex sympathetic dystrophy must be suspected when there is evidence of vasomotor instability, edema of the hand, tenderness over the metacarpophalangeal joints, or dystrophic skin changes. A triple-phase bone scan may show periarticular uptake in the wrist and metacarpophalangeal joints of the involved hand. Management includes range-of-motion exercises, optimal positioning of the upper limb, avoiding painful stimuli, and treating with nonsteroidal anti-inflammatory drugs when there is no medical contraindication. Other modalities, including transcutaneous electrical nerve stimulation or ultrasound therapy, may help to decrease pain and increase sensory feedback during recovery. A short course of oral steroids or the administration of a stellate ganglion block may decrease pain and symptoms. Better results have been reported in patients with positive bone scans who have completed a course of corticosteroids.

Central pain is rare, and the exact pathophysiology remains uncertain. Pain is often burning in character and is associated with an unpleasant sensation of tingling or "pins and needles." Other pain descriptions have been reported. Frequently the pain is spontaneous or evoked by touch. Central pain is difficult to treat. The use of narcotic analgesics frequently provides inadequate relief. Tricyclic antidepressants have been reported to have a beneficial effect. Other treatment alternatives include sympathetic blockade, guanethidine block, and neurosurgical ablative procedures.

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Acute Ankle and Foot Injury—Guidelines for Radiography

In this decade of increasing litigation, many clinicians faced with acute ankle and foot trauma automatically take radiographs in search of occult fractures. This practice raises costs and causes substantial delays in care. Recent prospective controlled studies of adult patients have identified aspects of a medical history and physical examination that correlate well with the presence (and also absence) of ankle or foot fractures. Coined the "Ottawa ankle rules," validated guidelines are derived from many methodologic standards. Because of the current low yield of ankle and foot radiographs—15% of all such x-ray films reveal fractures—the stage is set for reliable and cost-effective management of local ankle and foot trauma.

An ankle radiographic series is always indicated if an interview with the patient elicits a description of pain over the malleoli and also one of the following: inability to bear weight both immediately and on first evaluation by a physician (weight bearing is tested by asking the patient to take four consecutive steps without assistance); bone tenderness on palpation of the distal 6-cm posterior edge (tip) of the medial malleolus; or bone tenderness on palpation of the distal 6-cm posterior edge (tip) of the lateral malleolus. In related studies, this approach has detected all notable ankle fractures, allowing an examiner to forgo radiographs in 34% of patients.

A radiographic series of the foot is always indicated if the interview elicits a subjective complaint of pain in the midfoot zone and also one of the following: inability to bear weight both immediately and on first evaluation by a physician; bone tenderness on palpation of the navicular bone; or bone tenderness on palpation of the base of the fifth metatarsal. In related studies, the potential to reduce the number of foot films is 30% without increasing the chance of missed fractures.

An ankle or foot x-ray film series is also recommended when assessment of a patient is difficult because the patient is intoxicated or has a head injury, multiple painful injuries, or diminished sensation due to a neurologic deficit. Combined with proper follow-up for patients who do not improve within five to seven days, these principles can virtually eliminate the possibility of a missed fracture.

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Influence of Disability on Pregnancy and Motherhood

In the past, professionals often discouraged motherhood in women with disabilities. Innovative approaches have recently emerged that acknowledge each woman's understanding of her bodily functions, respect the ingenuity of other mothers who have adapted to similar disabilities, and integrate their unique blend of experience with the knowledge and skills of primary care physicians and disability specialists.

All medical services, childbirth, and exercise classes are provided in architecturally accessible offices, clinics, and hospitals. Examining tables have the potential to be lowered for easy transfer. Assistance is available for transfers, donning and doffing prostheses and braces, and for self-catheterization. A wheelchair-accessible scale is used, when required, to monitor weight during the course of pregnancy. When home visits and home birth are used, environmental accessibility is almost always assured.

Because the lithotomy position is difficult for many women with limited mobility, options are provided for pelvic examination without stirrups, in the supine, knee-chest, or side-lying position, or in a reclining wheelchair. Autonomic hyperreflexia—sudden, severe hypertension due to exaggerated sympathetic discharge in women with spinal cord injuries at or above T-6—is likely to be less severe if the woman is in a semisitting position for a pelvic examination. The application of anesthetic gel to the vagina and speculum may further lessen the chances of severe hyperreflexia.

Consideration is given to the interaction between the pregnancy and the disability. The fatigue of pregnancy can be especially severe for women with rheumatoid arthritis, multiple sclerosis, or chronic fatigue syndrome; nausea and vomiting may be particularly difficult for women with limited mobility; and women with respiratory insufficiency may have progressive difficulty breathing as pressure from the uterus increases, requiring ventilatory support during late pregnancy or labor. If bladder control is a problem before the pregnancy, it is likely to worsen as the growing fetus begins to press on the urinary bladder. Supplemental iron may cause severe constipation in women with neurogenic bowel problems. Nutritional assessment is needed to consider each woman's unique energy requirements, as well as the calories required for pregnancy and lactation. As the abdomen enlarges and the center of gravity shifts, there may be a need for a new or larger wheelchair, additional adaptive equipment, or extra personal assistance.

For women with visual impairments, detailed descriptions of labor and delivery are helpful. All staff members must be alerted to introduce themselves to the woman by name and function at each interaction. When a woman has a hearing impairment, it is important for office and hospital staff to ascertain what method of communication is most effective for her—writing, wearing a hearing aid, lip reading, or using a sign-language interpreter. To facilitate lip reading, a transparent mask can be used. At the woman's request, a family member, friend, or sign-language interpreter should be permitted to assist communication at all times, including during labor and delivery. Because few obstetricians have experience with patients with disabilities, it is important for the obstetrician to confer with the woman's disability specialist.

Touring the birth facility enables prospective mothers to evaluate whether the environment will meet their needs and, if not, what adaptations would be helpful. Women with hearing or visual impairments may do better in a room within direct sight or sound of the nurses' station. Women with mobility impairments may require electric controls on the hospital bed, a special mattress, or an overhead trapeze bar. For wheelchair users, toilets and showers must be accessible and adapted for safety and effective functioning. Caution should be exercised with routine procedures, such as the insertion of an intravenous line in the intact arm of a hemiplegic woman, as this may interfere with bed mobility and wheelchair transfers.

The recognition of the onset of labor may be difficult in women with impaired sensory innervation to the uterus (T-10 to T-12). Atypical or unexpected symptoms may occur such as abdominal or leg spasms, shortness of breath, urinary frequency every few minutes, or a headache with each contraction. Finding a good position for labor can be challenging. Decubitus ulcers can be avoided by alternating the sitting, reclining, and side-lying positions and by using padding. A woman may stay in her wheelchair until she reaches the delivery room. Although muscle weakness may make it impossible for the woman to assist in pushing the baby out, paralysis is not an indication for cesarean delivery, which should be considered only when a valid obstetrical indication exists. Hypotonia of the pelvic floor musculature may actually facilitate vaginal delivery.

Perineal distension, vaginal instrumentation, augmentation with oxytocin, amniotomy, and the labor itself may precipitate autonomic hyperreflexia in women with spinal cord injury at the T-6 or higher level. This can lead to hypertensive encephalopathy, cerebrovascular accident, intraventricular and retinal hemorrhage, and death. Uteroplacental vasoconstriction may result in fetal hypoxemia. Therefore, continuous monitoring of maternal blood pressure and cardiac rhythm is mandatory during labor in all patients at risk for autonomic hyperreflexia. In women with respiratory muscle weakness, blood gas levels should be evaluated before labor and pulse oximetry monitored during labor. Epidural or spinal anesthesia extending to the T-10 level is an effective preventive measure as labor progresses. If autonomic hyperreflexia occurs before or despite the use of regional anesthesia, hypertension may be treated with rapid-onset antihypertensive agents such as sodium nitroprusside or nitroglycerin, ganglionic blocking agents (trimethaphan camsylate), adrenergic blocking agents (guanethidine sulfate), or a direct vasodilator (hydralazine hydrochloride). During the second stage of labor, delivery can be expedited by using forceps or vacuum extraction. If dysreflexia cannot be controlled, a cesarean delivery under adequate anesthesia may be

required. Nonabsorbable sutures should be used for an episiotomy in women who are insensate in the perineum or spend their day sitting in a wheelchair. The wound should be examined frequently for breakdown.

The medical aspects of disability should not take precedence over the focus of pregnancy. Nightmares—for example, that a baby may be born without a spinal cord—can be relieved by providing information and reassurance that an acquired disability such as spinal cord injury cannot be transmitted to the baby. Through planning and organization, the woman's self-confidence can be affirmed and her abilities enhanced for the care of a dependent infant.

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Birth Brachial Plexus Injury

BIRTH BRACHIAL PLEXUS INJURY occurs in approximately 1 per 1,000 live births in the United States. The most frequently involved level of lesion is C5-6, causing Erb's palsy. The next most frequent is a combined palsy that includes C-7. Klumpke's paralysis, involving C-8 to T-1, is the least frequently seen. Most infants are large and born to multiparous mothers. Most (50% to 90%) of these lesions resolve spontaneously.

Evaluating a case of birth brachial plexus palsy can include physical, electrodiagnostic, and radiographic examinations. Radiographic examinations include x-ray films of the humerus and clavicle to exclude fractures, with controversy over the benefit of magnetic resonance imaging or computed tomography. Electrodiagnosis consists of nerve conduction studies, both motor and sensory, electromyography, and possibly somatosensory evoked potentials. Which muscles and nerves to examine should be carefully planned, depending on the areas of deficit. The somatosensory evoked potentials are done infrequently because infants must be sedated for the study. Instead, the proximal portions of the nerve are studied using F waves and H reflexes in nerve conduction studies. In an insensate arm, the presence of sensory nerve action potentials indicates an avulsion and that the lesion is proximal to the dorsal root ganglion. Fibrillations in paraspinal muscles may also indicate a preganglionic lesion, as these muscles are innervated by the posterior primary rami (as opposed to anterior primary rami innervating the arm). Fibrillations are not always present, however, and the overlap of levels of innervation also makes interpretation uncertain. The physical examination is done by observing any spontaneous use of the arm, positioning, the use of primitive reflexes, and positive and negative stimuli (offering candy and sharp or dull testing, respectively).

The initial treatment approach begins with occupational therapy. Parents are immediately taught range-of-motion exercises and maximal positioning of the involved upper extremity. Range of motion is used for maintaining mobility of the joints and to avoid contractures. This is of utmost importance whether the patient has spontaneous resolution of symptoms or if there is a need for surgical therapy in the future. Range-of-motion exercises in patients with Erb's palsy particularly emphasize abduction and external rotation of the shoulder along with supination of the forearm because of the classic adducted, internally rotated position of the arm with pronation of the forearm. In addition, extension and flexion of the elbow are done. In an infant with Klumpke's paralysis, the emphasis is on wrist and finger exercises and elbow extension range of motion. Splinting is used if there is severe wrist drop, particularly with unopposed strong wrist flexor muscles. Many infants, particularly babies with an insensate limb, require various forms of stimulation to increase the awareness of the involved extremity. In such a case, a bracelet with bells or other noise-making objects are frequently used so that the baby can "hear" the presence of the involved arm. Small toys may also be attached to a bracelet on that arm to improve attention to the limb.

It is important that any active motor function present in the involved extremity be used to its fullest. Parents are taught by a therapist how to enhance any motor function present in the limb, which varies depending on the level of injury. In a C5-6 injury, if only the hand has intact motor function, the arm must be positioned so that the hand can be actively used. If the proximal portion of the arm is functioning, but not the hand, then the child may use the arm for carrying large objects such as a stuffed animal or a beach ball, using the involved or both extremities. It is important to have the child perform these activities so that he or she learns to do some actions using both extremities and does not go through early developmental stages learning to do everything with one hand. If this occurs, it is extremely difficult to get the child to use both hands in the future, even if there is excellent motor and sensory return.

Problem areas noted in children with birth brachial plexus injury include the classic internal rotation and adducted contracted position of the arm of a child with C5-6 palsy who has had no range-of-motion exercises. With these exercises, there is a risk of dislocating the shoulder due to the shallow glenoid cavity and the minimal musculature present to hold the humerus into the shoulder. With range-of-motion exercises of the forearm to supinate, there is also a risk of dislocating the radial head. With no therapy or exercises, there may be contractures, muscle atrophy, and possible lack of use of the extremity, even if there is future motor return. Problems may include cosmetic problems with contractures, limb length discrepancy with the involved arm being shorter than the other, and winging of the scapula, although this may be less no-

ticeable as a child ages. Skin ulcerations may occur in an insensate limb from injury or even from children biting themselves. Pain is not usually present, unlike with acquired brachial plexus injuries in adults.

In babies without spontaneous resolution of their brachial plexus palsy, a surgical exploration can be considered after 4 months of age. Opinions of the optimal time for surgical interventions vary from 3 months to 9 months of age. The brachial plexus is surgically exposed, electrodiagnostic studies are done (somatosensory evoked potentials and nerve conduction studies), and then a neurolysis (removing scar tissue on the nerve) and, in some children, a nerve graft are done. Improvements are noted from six months to two years after the operation. In children older than 3 years who have substantial deficits, tendon or muscle transfers can be done to improve function. Tendon transfers are most commonly used about the wrist. Muscle transfers can be used to provide elbow flexion or extension and shoulder abduction and external rotation. The child must be able to cooperate with intensive therapy after a muscle transfer to learn to use the new muscle function.

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Alerts, Notices, and Case Reports

Urticarial Skin Lesions and Polymyositis Due to Lymphocytic Vasculitis

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URTICARIA IS a common disorder in the general population. Approximately 20% of people have acute urticaria at least once during their lifetime.[1] The differential diagnosis of urticaria can be extensive. Urticariogenic factors can be grouped into several categories, including physical agents, contactants, ingestants, inhalants, infections, systemic diseases, and psychogenic factors.[2] Within the category of systemic diseases, an important possibility is vasculitis.

When vasculitis causes an urticarial skin eruption, the histopathologic study of a biopsy specimen usually reveals leukocytoclastic vasculitis.[3] Other types of vasculitis, however, are occasionally documented by histopathologic studies of biopsy specimens taken from active skin lesions. For example, hypocomplementemic urticarial vasculitis syndrome (HUVS) may develop in patients with high titers of C1q precipitins in the serum.[4] We present here the findings in an adult with long-standing urticarial skin lesions resulting not from leukocytoclastic vasculitis or HUVS, but from a lymphocytic vasculitis.

Report of a Case

The patient, a 49-year-old woman, was referred for the evaluation of urticarial skin lesions of three years' duration. The lesions typically began in the evening and were accompanied by a burning sensation rather than pruritus. The lesions generally lasted 48 to 96 hours and healed with hyperpigmentation. After an asymptomatic interval of four to five days, another cycle would occur. Her condition had steadily worsened during the year before the evaluation. Although antihistamines did not relieve her skin discomfort, oral corticosteroids at high doses were effective. Ten months before the evaluation, daily treatment with prednisone, 10 mg taken each morning, was initiated. This treatment reduced the occurrence of the skin lesions but did not eliminate them.

(Kao NL, Zeitz HJ: Urticarial skin lesions and polymyositis due to lymphocytic vasculitis. West J Med 1995; 162:156-158)

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Her medical history revealed that 14 years before the evaluation, she was admitted to hospital for treatment of a right middle lobe pneumonia that failed to clear with antibiotic therapy. Lymph node biopsy specimens showed noncaseating granulomas consistent with sarcoidosis. She received treatment with prednisone for four years and had not had any reactivation of sarcoidosis after the prednisone was discontinued. Two years before the evaluation, after a vaginal hysterectomy, treatment with estrogen and calcium supplements was initiated. She had no known allergies. She denied alcohol or drug abuse. She was employed as an insurance agent and had no known exposures to occupational toxins or allergens. She smoked six to eight cigarettes daily for 30 years. Her family history was remarkable for atopic disorders. The review of systems revealed fatigue, curved fingernails, and weakness of her arms and legs, particularly proximally.

On physical examination, the patient's skin had slightly raised, red, 5-mm^2, irregularly shaped lesions on her head that blanched with pressure. Her anterior cervical lymph nodes were mildly enlarged. Her nails were moderately clubbed. The strength of extremity muscles, particularly proximal muscles, was mildly reduced. The remainder of the physical examination showed no abnormalities.

The results of initial laboratory studies, including a complete blood count, platelet count, urinalysis, syphilis serologic test, antinuclear antibodies, complement profile, circulating immune complex assays, hepatitis virus (A, B, and C) serologic tests, cryoglobulins, and serum angiotensin I-converting enzyme level, were within normal limits. The erythrocyte sedimentation rate was 35 mm per hour (normal, 0 to 20). Serum chemistry levels revealed modest elevations of alanine aminotransferase (103 U per liter; normal, 0 to 55) and lactate dehydrogenase (450 U per liter; normal, 0 to 270). There were notable elevations of creatine kinase (4,945 U per liter; normal, 45 to 235) and aldolase levels (51 U per liter; normal, 1 to 8). Creatine kinase isoenzyme analysis documented skeletal muscle as the site of origin of the elevated serum creatine kinase level.

Based on the clinical and laboratory findings, skin and muscle biopsies were done. Both biopsy specimens showed lymphocytic vasculitis (Figure 1). Specifically, there was a lymphocytic inflammatory infiltrate centered around and in blood vessels with fibrinoid changes in the vessel walls. Some infiltrate extended into the surrounding connective tissue. There was little infiltrate in muscle fibers. Immunofluorescence stains of skin tissue and several special stains of muscle tissue were uniformly normal. Additional laboratory tests, including phenotyping lymphocytes for surface membrane immunoglobulin, CD19, CD20, CD3, CD4, CD8, CD16, CD56, HLA-DR, and CD10 plus CD5 to exclude a lymphoma; Jo-1 antibody titers; and serologic tests for toxoplasmosis,

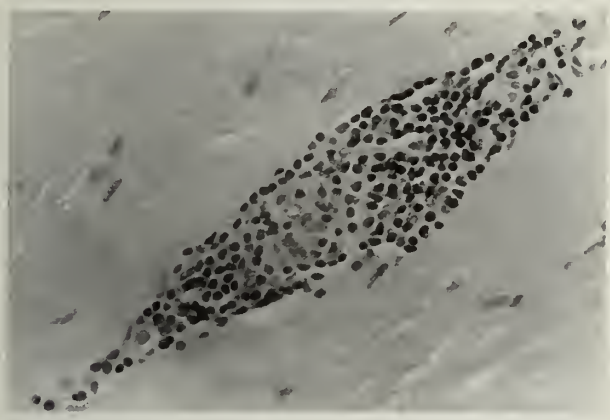

Figure 1.—The vessel wall has a lymphocytic infiltrate that extends also into the perimysial connective tissue (hematoxylin and eosin stain, original magnification × 200).

human immunodeficiency virus, and Lyme disease were negative.

The final diagnosis was idiopathic lymphocytic vasculitis with secondary urticarial skin lesions and polymyositis. The prednisone dose was increased to 40 mg by mouth each morning. Although the skin lesions vanished quickly, the fatigue, myalgias, and weakness resolved slowly during the first eight weeks of treatment. Various laboratory values decreased to the normal range over three months (Table 1). The daily prednisone dose was tapered by 5 mg per month; even after the dose was reduced to 11 mg daily, the vasculitis continued to be quiescent by clinical measurements, although the erythrocyte sedimentation rate increased slightly.

Discussion

Although many diseases produce skin discomfort, urticaria is distinguished by pruritic wheals that resolve completely. Lesions may be referred to as urticarial if they have characteristics such as persistence beyond 24 hours, burning, pain, or sequelae (such as hyperpigmentation or scarring). The differential diagnosis of urticarial skin lesions frequently focuses on vasculitis (including HUVS) and autoimmune diseases, but includes thyroid disorders and viral infections (such as hepatitis B). When clinicians evaluate urticarial lesions to diagnose or exclude vasculitis, they should obtain a biopsy of skin.

Vasculitis, like many other systemic diseases, frequently has diverse manifestations. Therefore, it can be included in the differential diagnosis of almost any sign or symptom. Microscopic studies of a vasculitic skin lesion demonstrate leukocytes infiltrating the walls of affected vessels. In most vasculitic syndromes, these cells are predominantly neutrophils and the complement system is activated. This activation can be detected in the blood as hypocomplementemia, circulating immune complexes, and on microscopy, fibrinoid degradation. In a few patients, however, the number of lymphocytes exceeds the number of neutrophils, and there is no evidence of complement activation.[5] In these patients, the initial diagnosis is lymphocytic vasculitis.

In the case reported here, the pathologic process identified histologically as lymphocytic vasculitis was

TABLE 1.—*Response of Laboratory Values to Oral Steroid Therapy*

	Laboratory Values		
Treatment Week	Creatine Kinase, U/liter*	Erythrocyte Sedimentation Rate, mm/hr†	Prednisone Dose, mg each AM
0	4,945	35	3
1	4,613	--	40
5	2,134	--	40
6	1,158	--	40
7	465	10	40
10	93	23	35
15	30	20	35
18	13	34	30
29	26	29	25
33	26	13	20
46	21	27	15
54	27	24	14
62	28	46	13
78	33	39	11

*Normal, 45 to 235 U per liter.
†Normal, 0 to 20 mm per hour.

TABLE 2.—*Clinical Conditions Associated With Lymphocytic Vasculitis*

Conditions with known cause
Adverse drug reactions
Necrobiosis lipoidica diabeticorum
Nodular scabies
Insect bites
Viral infections
Rickettsial infections
Spirochetal infections—syphilis
Lepromatous leprosy

Conditions without known cause
Pigmented purpuric eruptions
Lymphomatoid granulomatosis
Angiocentric immunoproliferative lesion
Wegener's granulomatosis
Sarcoidosis
Behçet's disease
Systemic lupus erythematosus
Sjögren's syndrome
α_1-Antitrypsin deficiency panniculitis

Dermatologic reaction patterns
Urticaria
Hypocomplementemic urticarial vasculitis syndrome
Erythema multiforme
Pityriasis lichenoides et varioliformis acuta
Lymphomatoid papulosis
Erythema perstans
Granuloma annulare
Pyoderma gangrenosum

responsible for the urticarial skin eruption that was the presenting symptom. Further clinical evaluation showed that the lymphocytic vasculitis also was responsible for the polymyositis that had been identified on physical examination and confirmed by serum enzyme levels. The cause of polymyositis, an inflammatory process affecting symmetrical skeletal muscle groups, is identified only in some patients.[6] Causative agents include adverse reactions to ingestants, autoimmune diseases, malignant neoplasms, sarcoidosis,[7-9] and vasculitis.[10] Although our patient had well-documented sarcoidosis in the past, our clinical, serologic, and histologic evaluation failed to provide any evidence of reactivation of her previous disorder. Thus, to our knowledge, this is the first reported case of a lymphocytic vasculitis producing both polymyositis and urticarial skin lesions.

The differential diagnosis of a lymphocytic vasculitis includes autoimmune diseases, infections, malignant neoplasms, adverse reactions to ingestants, and inflammatory disorders of unknown origin (Table 2).[11-15] When the cause of lymphocytic vasculitis is known, the underlying cause should be removed or treated. Patients such as the one reported here with an unidentified etiologic factor frequently require treatment with anti-inflammatory medication, which may include corticosteroids, azathioprine, and cyclophosphamide. When these medications are used, the lymphocytic vasculitis is usually well controlled.

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Impotence Related to Anabolic Steroid Use in a Body Builder

Response to Clomiphene Citrate

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THE RECREATIONAL USE of anabolic steroids has become commonplace among athletes.[1,2] Exercise enthusiasts frequently subscribe to information from such sources as the "Underground Steroid Handbook"[3] and self-design illicit drug therapy, including the use of human chorionic gonadotropin (hCG), clomiphene citrate (Clomid), and tamoxifen citrate, to counter the side effects of gynecomastia and reduced testicular volume. Despite this apparent drug sophistication, not only can these persons have a psychological dependence on the anabolic steroids,[4,5] but hypogonadotropic hypogonadism that lasts for months[6,7] to years[8] may also develop.

The case presented here illustrates the degree of drug knowledge among body builders, the psychosocial dependence on these drugs, and the potential of clomiphene[9] in treating the disorder of pituitary-gonadal failure in such persons.

Report of a Case

The patient, a 29-year-old man, had impotence and decreased libido for a year. He is a college student and a competitive body builder who had used anabolic steroids for eight months (January to August 1992), alternating 16-week cycles of testosterone cypionate (Depo-Testosterone), 1,500 to 1,800 mg per week, and oxymetholone (Anadrol), 560 mg per week. After stopping the use of these drugs in August 1992, he was impotent with no spontaneous erections and had diminished libido. He completed a self-selected four-week trial of human chorionic gonadotropin (hCG) in September 1992 without any change in libido and no improvement in potency. The dose of hCG is unknown, and the patient denied any previous use of the drug. He was advised by colleagues to take a course of clomiphene or await the spontaneous return of sexual

(Bickelman C, Ferries L, Eaton RP: Impotence related to anabolic steroid use in a body builder—Response to clomiphene citrate. West J Med 1995; 162:158-160)

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
Gn-RH = gonadotropin-releasing hormone
hCG = human chorionic gonadotropin
LH = luteinizing hormone

function. He elected to wait for nine months, without success.

He sought endocrine consultation in July 1993, almost a full year after his last steroid dose, because of continued impotence and reduced libido. On examination he was robust, weighing 76 kg (168 lb), height 178 cm (5 ft 10 in), appearing healthy, and was heavily muscled. He had a reduced testicular volume of 10 ml on both sides and 2 cm of gynecomastia on both sides. A urine screening test for exogenous anabolic steroids was negative for 19 steroids or metabolites, including danazol, fluoxymesterone, methyltestosterone, 19-nortestosterone, oxymetholone, and stanozolol, as well as the diuretic probenecid. An adrenocorticotropic hormone-stimulation test showed a normal rise in the cortisol level from 360 to 830 nmol per liter (13 to 30 μg per dl). Magnetic resonance imaging with gadolinium enhancement revealed a normal pituitary gland. Serum gonadotropin and free testosterone levels were abnormal, however, as shown in Figure 1, with a follicle-stimulating hormone (FSH) level of 0.6 mIU per ml (1.6 to 17.8 mIU per ml), a luteinizing hormone (LH) level of 1.9 mIU per ml (1.4 to 11.1 mIU per ml), and a free testosterone level of 7.1 pg per ml (19.0 to 41.0 pg per ml).

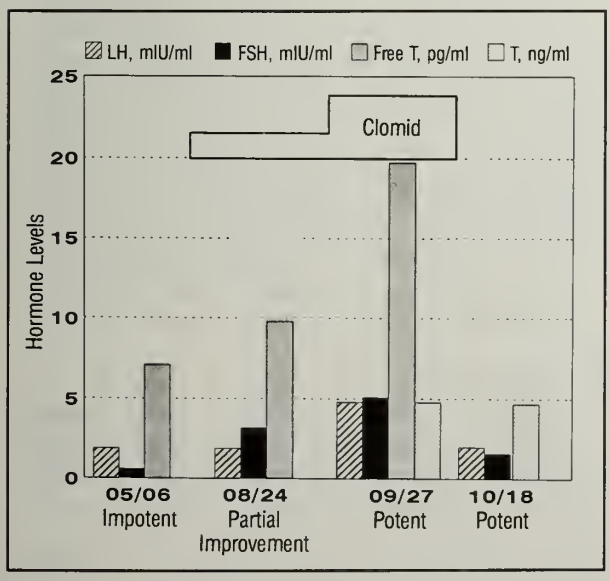

Figure 1.—The 5-month course of response to Clomid (clomiphene citrate) is represented by serial plasma levels of pituitary gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), gonadal free testosterone (Free T), and total testosterone (T). The associated improvement in sexual potency is seen to parallel the rise in free and total testosterone levels in response to Clomid therapy.

Treatment was initiated with clomiphene, 50 mg orally per day, and after a month of therapy he had noticed no improvement in potency or libido, although he had begun having morning erections. Serum hormone tests showed moderate improvement in FSH, LH, and free testosterone levels, although not in the normal range (Figure 1). A month after taking a double dose of clomiphene (100 mg per day), the patient reported an increase in libido and potency, and he was able to have sexual intercourse daily. His gonadal volume was unchanged, although serum FSH, LH, and free testosterone levels had reached normal for his age (Figure 1). After clomiphene therapy was discontinued three weeks later, the serum FSH and LH levels fell to normal, and the total serum testosterone remained at a normal level of 16.3 nmol per liter (4.7 ng per ml) (range, 12.5 to 34.5 nmol per liter [3.6 to 9.9 ng per ml]). This response suggested a restoration of normal hypothalamic-pituitary-gonadal function, and it was proposed to reevaluate this function with a longer follow-up to determine whether the correction was sustained.

Follow-up of the patient six months later revealed that he had returned to the illicit use of Depo-Testosterone at 400 mg per week to achieve a level of sexual performance three times that achieved with clomiphene alone. He noted that his testes were smaller, and he was considering trying another course of hCG in combination with tamoxifen to prevent worsening gynecomastia.

Discussion

The illicit use of anabolic steroids is becoming more widespread, especially among those involved in competitive athletics or body building and even among teenagers.[10] Even when gonadal dysfunction occurs, persons often continue using the anabolic steroids, in part because of the neuropsychiatric effects, which include psychotic symptoms, affective syndromes, increased aggression, and psychological dependence.[4,11] In lay literature, it is common to find medical discussions and advertisements concerning anabolic steroids, androgen supplements, and agents used to combat the side effects of gynecomastia, hirsutism, fluid retention, and acne (*MuscleMag International*, September 1994, pp 280-281).

Most synthetic anabolic steroids have some androgenic effects that inhibit gonadotropin-releasing hormone (GnRH) release from the hypothalamus and FSH and LH release from the anterior pituitary. This results in a hypogonadotropic state, and if the agents are used for a prolonged period, testicular atrophy with reduced serum testosterone levels results, causing reduced libido and impotence. When their use is discontinued, the feedback inhibition of GnRH, FSH, and LH synthesis and release is removed and the hypogonadotropic hypogonadism is expected to resolve. According to the literature reports,[5-7] this usually occurs within four months. Only two cases have been reported in which suppression of the hypothalamic-pituitary-testicular axis lasted

longer than four months.[7] The first of these patients was administered hCG, and the outcome was determined to be successful when his wife conceived. The second patient presented with decreased libido three years after his last use of anabolic steroid and was found to have a severely blunted response to a GnRH-stimulation test, consistent with hypothalamic-pituitary suppression.

The patient in the case reported here is unique not only in the year-long suppression of his hypothalamic-pituitary-gonadal axis, but also in the successful response to hypothalamic-pituitary stimulation with clomiphene. Although we do not know his gonadotropin and testosterone levels before he began using steroids, it is unlikely he had a preexisting GnRH-deficiency state (such as Kallmann's syndrome) as he had normal secondary sexual development of phallus and hair distribution before initiating exogenous steroid use. We assume that he was compliant in abstaining from exogenous steroids during the treatment period, based on the negative drug screen and compliance with clomiphene administration. More frequent, random screening would be needed to confirm this assumption. The self-administration of hCG should have elicited a testosterone response, but it is uncertain whether he received true hCG in adequate dosage. Because he perceived the failure of a self-initiated hCG trial, we opted for the use of clomiphene at dosages commonly used in women with hypothalamic-pituitary-ovarian failure. Clomiphene use has previously been reported for the treatment of men who, during evaluation for infertility, are found to have marginal testicular failure or poor gonadotropin production.[8] Clomiphene appears to produce an antiestrogen effect on the hypothalamus that results in increased GnRH release. In addition, clomiphene exerts an estrogenlike effect on the pituitary, increasing pituitary sensitivity to GnRH.[12]

We propose that with the use of clomiphene we were able to augment the hypothalamic and pituitary responses to his low but not absent ambient estrogen derived by aromatization from testosterone. This is the first reported case of clomiphene-induced restoration of FSH, LH, and free testosterone levels in a man with recreational steroid-induced pituitary-gonadal failure.

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Lead Poisoning in a Radiator Repairer

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More than 1.4 million workers in the United States are at risk of exposure to lead in industries as diverse as radiator repair, construction, demolition, lead smelting, casting, foundry, and manufacture of stained glass or batteries.[1] Scientists have been aware of the toxic effects of lead since ancient times.[2-7] In 1978 this copious scientific knowledge led to the enactment of a comprehensive lead standard by the United States Occupational Safety and Health Administration (OSHA).[6] Unfortunately, compliance with this standard may be inadequate even today, as is exemplified by this urban case of lead poisoning in a radiator repairer.

Report of a Case

The patient, a 26-year-old man, was seen because of slight fatigue, headaches, episodic nausea, reduced sex drive, excessive sleepiness (for as long as 12 hours a day), excessive loss of scalp hair, and weakness of both upper extremities. He had frequent slight scalp burning that required shaving of the scalp. Coital frequency declined from 12 to 3 times a month. He did not have abdominal pain or constipation. He had never smoked and rarely consumed alcohol. He had two children aged 1 and 7 years; it required three years of unprotected sex for his second baby's conception (his wife was 24 years old and healthy). In 1991 he had a ureteral stone.

Occupational History

The patient had been a radiator repairer (standard industrial classification code 7539) for seven years. He repaired 15 to 20 automobile radiators a day in a small, poorly ventilated shop. He worked unsupervised as a lone

(Lohiya GS, Lohiya S: Lead poisoning in a radiator repairer. West J Med 1995; 162:160-164)

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TABLE 1.—*Blood Lead Levels and Related Tests by Days Since Medical Removal From Occupational Lead Exposure**

	Laboratory Values†				
	Blood Lead				
Day	SI Units, μmol/liter	Canventianal Units, μg/dl‡	Zinc Protaparphyrin, μg/dl	Hematocrit, %	Hemoglobin, grams/liter
0	2.42	50.2	94§	45.1	151
28	2.89	59.9	--	41.1	145
35	2.54	52.7	--	--	--
59	2.94	61.0	--	--	--
74	2.84	59.0	--	41.0	143
106	2.07	43.0	--	--	--
113	1.59	33.0	--	--	--
147	1.78	37.0	48	44.1	147

SI = Système International

*Patient received oral chelation therapy with succimer, 500 mg twice a day, from day 94 through day 107.
†Normal reference values: lead, <1 μmol/liter (<20 μg/dl); zinc protoporphyrin, <70 μg/dl; hematocrit, 42% to 52%; hemoglobin, 135 to 169 grams/liter.
‡Lead unit conversion factor: 1 μg/dl = 0.04826 μmol/liter; 1 μmol/liter = 20.72 μg/dl.
§On day 0, the free erythrocyte protoporphyrin level was determined instead of the zinc protoporphyrin level (normal <35 μg/dl).

employee, 48 hours a week. He dry-swept the concrete floor that had many crevices, generating lead dust. He ate while working, without hand washing; he did not shower or change clothes after work. He had no nonoccupational exposure to lead from lead-glazed pottery, moonshine whiskey, herbs, aphrodisiacs, retained lead bullets, gasoline sniffing, pica, peeling wall paint, or hobbies.

The patient disassembled old radiators by melting the solder joints using a handheld acetylene torch heated to 300°C (572°F). He cleaned the radiator end cap with pressurized air in an abrasive bead-blaster cabinet that lacked exhaust ventilation. When he opened the bead blaster, lead dust emanated. He cleaned the bead-blaster filters with a wire brush, generating more lead dust. He soldered radiators using a metallic wire (60% lead and 40% tin; Dutch Boy Solder, Taracorp Industries Inc, Granite City, Illinois) and inhaled the fumes. Sometimes his hands got burned by hot solder particles. He used no respirator, gloves, mask, or goggles. He received no education about lead hazards and had no biologic or environmental monitoring.

Laboratory Tests

In trace metal tubes containing lithium heparin (Becton Dickinson Vacutainer Systems, Franklin Lakes, New Jersey), 5 ml of venous blood was collected. It was analyzed for lead by atomic absorption in an OSHA-approved laboratory (Medico Laboratories, Santa Ana, California); a low lead calibration procedure was used. Serial grip strengths were recorded by a Jamar Adjustable Dynamometer (Asimow Engineering, Los Angeles, California) with the handle in the middle (third) position. A semen specimen was collected in the office (after the patient had abstained from sexual intercourse for a week) by having him masturbate in a sterile plastic cup. After a 15-minute wait to permit liquefaction, the number of spermatozoa was counted in a Makler chamber; motility was checked sequentially in each row initially and after one, two, and three hours.

Results

The patient weighed 67 kg (148 lb) and measured 1.75 m (5 ft 9 in). His blood pressure was 110/70 mm of mercury. He had mild male-pattern frontal alopecia and good hygiene. There was no Burton's line on the gums; the fingernails were clean. Grip strength on day 0 was 25, 24, and 22 (mean, 23.7) kg in the right (dominant) hand and 20, 20, and 18 (mean, 19.3) kg in the left hand; it progressively improved to 34, 36, and 32 (mean, 34) kg and 30, 30, and 30 (mean, 30) kg, respectively, on day 147. A review of systems and the results of a neurologic examination were normal.

The initial (day 0) blood lead concentration was 2.42 μmol per liter (50.2 μg per dl), and the free erythrocyte protoporphyrin level was 94 μg per dl (normal < 35 μg per dl) (Table 1). There was no anemia or basophilic stippling of erythrocytes; the sedimentation rate was 18 mm per hour (normal, 1 to 10 mm per hour). All serum chemistry values measured by automated panel were normal. The results of urinalysis, creatinine clearance, and levels of blood urea nitrogen, serum thyroxine, creatinine, testosterone, urine lead, and urine protein were normal (Table 2). An examination of the semen specimen showed reduced volume and sperm motility, an increased number of spermatozoa with deformed heads, and abnormal cytoplasmic inclusions (Table 3).

An electroneuromyogram was done by the disposable monopolar needle electrode technique. On day 11, it revealed bilateral radial motor mononeuropathy with primarily axonal involvement, without denervation. The radial motor nerve evoked-response amplitudes were substantially reduced on both sides (range, 0.839 to 3.86 mV) compared with the ulnar and median motor nerves (range, 10.1 to 11.5 mV); there were borderline bilateral

radial nerve F waves. On day 34, this study was normal.

On day 0, the patient was removed from work, but no reduction in his blood lead concentration occurred for 74 days. With informed consent, he was treated with oral succimer (meso 2,3-dimercaptosuccinic acid; Chemet, McNeil Consumer Products, Fort Washington, Pennsylvania), 500 mg twice a day, from day 94 to day 107. His blood lead concentration fell to 2.07 μmol per liter on day 106 and 1.58 μmol per liter on day 113 (Table 1).

Per California's Childhood Lead Poisoning Prevention Act of 1986, which requires notification of all blood lead concentrations higher than 1.21 μmol per liter (25 μg per dl), this case was reported to the California State Department of Health. An investigation was undertaken by its Occupational Lead Poisoning Prevention Program, and the following recommendations were made to the employer (Peter Scholz, MPH, associate industrial hygienist, written communication, November 23, 1993):

A lead medical surveillance program should be established under physician supervision. Lead exposure should be controlled by local exhaust ventilation, good housekeeping, employee hygiene, personal protective equipment, or use of lead-free solder. Exhaust ventilation should be installed on the bead blaster filtration cabinet and in the soldering area. Efficacy of local exhaust ventilation should be checked by watching the path of the visible plume or by installing a static pressure gauge and manometer on the exhaust hood. Cleaning with a wire brush should be discouraged. Before cleaning, filters should be lightly sprayed with water to suppress airborne dust. A properly fitted respirator (dual cartridge, elastomeric half-mask respirator equipped with high-efficiency particulate filters) should be worn when soldering or cleaning the filters. Dry sweeping of work areas should be stopped; a high-efficiency particulate vacuum should be used. Floor should be repaired to fill all holes. Employees should be required to clean hands, forearms, and face with water and soap before lunch and at the end of work. Persons exposed to airborne lead concentrations over 50 μg per cubic meter should shower at the end of shift. Periodic breathing zone air monitoring should be performed to assess if an employee is exposed to airborne lead above the action level of 30 μg per cubic meter.

TABLE 2.—*Biochemical Investigations Pertinent to Lead Exposure*

Substance	Patient Values SI Units	Patient Values (Canventiana Units)	Normal Reference Values
Creatinine clearance, ml/sec (ml/min)	1.2	(72)	70-140
Urine protein, grams/d (mg/24 hr)	0.05	(54)	< 165
Urine lead, μmol/d (μg/24 hr)	0.30	(63)	< 80
Serum creatinine, μmol/liter (mg/dl)	106	(1.2)	45-125 (0.5-1.4)
Blood urea nitrogen, mmol/liter (mg/dl)	5.35	(15)	1.75-7.0 (5-20)
Serum uric acid, μmol/liter (mg/dl)	333	(5.6)	215-460 (3.6-7.7)
Serum testosterone, nmol/liter (ng/ml)	17.0	(4.9)	7.6-31.0 (2.2-9.0)

SI = Système International

Discussion

Slight to moderate lead poisoning developed in this patient because of uncontrolled occupational exposure to lead for seven years. He inhaled lead fumes during soldering and burning of old solder and lead dust while cleaning radiator end caps in the bead blaster and while sweeping the floor.

This case vividly documents that compliance with the lead standard, 16 years after the enactment of federal standards, was poor in this radiator repair shop.[1-3,8] This case probably represents the tip of the iceberg because of the gross underreporting, due to nontesting, of elevated blood lead concentrations. One study found that legally required blood lead measurements were obtained in only 2% of the workplaces in California.[9] This observation is important for strategic planning and getting the best results from our limited prevention resources.

This case could have been prevented had there been compliance with the lead standard requirements of employee training, housekeeping, ventilation, personal hygiene facilities, biologic and environmental monitoring, and respirator usage. Such flagrant violation of the standard probably occurred because of five factors: employer ignorance, apathy, or unscrupulousness; employment of a nonunionized worker without vocational training; employee ignorance of the hazard; lack of a relationship with an occupational health physician; and lenient enforcement by OSHA, perhaps due to limited staffing. Industry-targeted, community-based outreach programs are required to attack these issues.

Compliance with the lead standard can probably be improved through the educational and inspectorial role of the workers' compensation insurer. The insurer should evaluate exposures and require evidence of compliance—such as blood lead measurements or environmental monitoring reports—as a condition for initial and continued insurance; it would be an economically wise business strategy for insurers because it would reduce claim expenses. Manufacturers of lead products should supply a brochure explaining the law and the end-users' responsibility for compliance.

For a small radiator shop, the cost of complying with the lead standard can amount to an unacceptably high proportion of its gross revenue; therefore, the use of lead-free copper-tin solder (Dutch Boy Lead Free

TABLE 3.—*Semen Analysis on Days 11 and 28*

Variable	Day 11	Day 28	Normal Values
Volume, ml	0.5	1.0	2-5
Liquefaction in 15 min	Partial	Partial	Full
Motility, %	62	64	> 70
Sperm count, million/ml	240	262	60-300
Normal sperm, %	63	74	80-90
Deformed heads, %	18	6	0-10
Double forms, %	2	0	0-10
Abnormal cytoplasmic inclusion, %	17	20	0-10

Solder, Taracorp Industries Inc) should be proactively encouraged. Such substitution would cause a minimal increase in soldering cost per radiator: lead-free, $4.35 per lb; leaded, $1.85 per lb (Karen Hipkins, NPC, written communication, July 13, 1994) while facilitating employer compliance with the standard.

The medical removal protection clause of the lead standard imposes a high financial burden on employers and should be touted as a reason for compliance. For common industrial disabilities, workers are compensated for only two thirds of regular (excluding overtime) wages; this is usually covered by the insurer. In contrast, workers with high blood lead concentrations are entitled to full wage (including overtime) and seniority benefits for as long as 18 months; employers have to personally make up wage loss not compensated by the insurer.[6]

The lead standard requires medical removal from lead exposure if blood lead concentrations are higher than 2.9 μmol per liter (60 μg per dl) on even one occasion or if blood lead concentrations have been higher than 2.4 μmol per liter (50 μg per dl) on three occasions at one-month intervals during the previous six months.[6] This patient was removed from lead exposure after a single blood lead level of 2.42 μmol per liter (without fulfilling the medical removal criteria) because of substantial clinical symptoms, the absence of previous baseline blood lead levels, and an obviously unsafe workplace. Because the employer had no alternative or modified lead-free work, the patient was placed on temporary total occupational disability.

In this patient, we used succimer as the chelator. Although the Food and Drug Administration has currently approved the use of succimer only for children, it has been used in adults effectively[10]; we were satisfied with its use and encountered no important side effects. Our choice of succimer was based on its ease of oral administration and relative lack of serious side effects. In contrast, the only other oral chelator, penicillamine, can cause serious renal and blood anomalies. Another chelator, calcium sodium edetate, has to be administered intravenously (requiring a costly 5-day hospital stay) or intramuscularly (painful); furthermore, it can cause serious renal or nervous toxicity by redistributing lead from bone to soft tissue. The fourth chelator, dimercaprol (also requiring intramuscular administration), can cause hypertension and gastrointestinal or nervous system toxicity.[3]

Under the lead standard, the primary treatment of lead intoxication is to stop the exposure. Prophylactic chelation therapy against the rise of blood lead levels is illegal.[7] With the availability of a relatively safe oral chelator, the fear has been expressed that employers may rely on chelation to reduce lead concentrations and the duration of medical removal. It has been suggested that the use of chelation should be reserved for persons with substantial symptoms or signs of lead toxicity.[5] Many supposedly "asymptomatic" persons, however, may have subtle evidence of disease, such as abnormal spermatogenesis, reduced intelligence quotient, or a subclinical reduction in hemoglobin levels.[11] Moreover, great gaps exist in our knowledge of the role of low-level lead exposure in causing chronic nervous dysfunction, hypertension, renal failure, and parkinsonism.[1,12] Lead is an enzyme poison, and it is the lead in the blood (not in the bone) that is damaging to the organs. Therefore, if blood lead concentrations are high, chelation is a wise choice, along with proactive enforcement of the lead standard.

This patient had evidence of sexual dysfunction (reduced sex drive, impotence, requiring three years for the conception of a baby, asthenospermia, and telospermia) and peripheral neuropathy (weakness of upper arms, reduced grip strength, and radial motor mononeuropathy on electroneuromyogram). These findings are consistent with earlier observations[5,12,13-15] and are important because of their occurrence at a blood lead concentration (2.94 μmol per liter) that may be encountered in industry.

Despite stopping occupational lead exposure for 74 days, this patient's blood lead level continued to increase. This apparent paradox probably reflects continuing re-equilibration of lead between blood and bones. Of total body lead, 90% is stored in bones where its half-life is 25 years[16]; the remaining 10% is found in blood (mainly in erythrocytes), with a half-life of 36 days.[14] As blood lead levels fall, some bone lead may be released into the blood. Blood lead levels are a poor indicator of cumulative exposure, and persons with widely divergent exposure may have similar levels. Therefore, in patients with ongoing lead exposure, a better estimate of the total body lead burden should be obtained by noninvasive K x-ray fluorescence of bones.[17]

This case illustrates the importance of taking a detailed occupational history, as emphasized by Dr Bernardino Ramazzini in 1733, "Ask your patient what is his occupation." This patient presented with nonspecific symptoms that can occur in a myriad of conditions; the diagnosis could have been missed, and the patient might have continued to receive exposure to lead, with possibly disastrous results.[8] Physicians owe it to themselves and society to identify occupational diseases that might otherwise be missed, particularly in small businesses that have no formal relationship with an occupational physician.

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Commentary

Scenarios for Success—Enhancing Women Physicians' Professional Advancement

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The distribution of women physicians among specialties remains uneven (Table 1). For example, 60% of the residents in pediatrics versus 17% in surgery are women. Growth in the proportion of women in academic medicine is apparent in virtually every department among residents, faculty, and full professors. Nonetheless, most schools do not have even one woman full professor in the specialties of obstetrics and gynecology, surgery, family practice, and anesthesiology. Whereas the percentage of women faculty in all specialties has been gradually climbing—in 1975 women were 10% of dermatology faculty; in 1994 this percentage was 29%—the proportion of these women attaining the rank of full professor has not risen. The proportion of all women faculty rising to the rank of professor remains below 10%, the same as in 1980; the proportion of men at this rank has likewise remained stable, but at about 32% during this interval. Thus, for women faculty in a number of disciplines, isolation remains a problem, especially at the higher ranks. Approximately 118 women currently head academic departments at medical schools in the United States—including interim chairs—with many schools having no women at this high rank.[1]

The only available longitudinal data are from a cohort study of all full-time medical school faculty whose first faculty appointment was in 1976. In 1991, more than twice the percentage of men (22%) as women (10%) faculty had reached the rank of professor.[2] In a national study of general internal medicine, cardiology, and rheumatology faculty, men and women had similar job descriptions and time allocated to clinical work, teaching, and research and similar academic productivity as measured by the number of grants, abstracts, and publications in refereed journals.[3] The rewards that women received, however, were not equivalent to those of men in compensation and rank.

The term "glass ceiling" is not helpful in understanding why more women are not advancing into policy-making and leadership positions. Ceiling implies that the powers-that-be are deliberately limiting the number of women moving ahead. In reality, many deans and department chairs are concerned about the paucity of women candidates for top positions.[4] As an aid to a discussion of the complex reasons why more women have not progressed further, it is helpful to consider a hypothetical case.

The Case of Dr New

Dr New, a 35-year-old cardiologist, has been encouraged since her internal medicine clerkship to devote herself to academic medicine. She has been an assistant professor on a tenure track for four years at Prestigious Medical Center. Her teaching evaluations and reputation with patients and staff are stellar. She is federally funded by an R01 research grant and is making good progress. Her difficulty is with Dr Key, the most high-powered professor in her section. Their research areas intersect so that they must work together occasionally. His manner with her tends to be characterized by one-upmanship games, and he pointedly does not include her when he gathers his laboratory staff or other section members for lunch. A nurse-friend informs Dr New that she has overheard Dr Key wondering aloud about whether Dr New could possibly be a good mother and what it would be like to be married to such a "ball buster" (referring to her handling of some misbehavior on the part of a resident). Dr New decides to try to ignore his antagonism.

When Dr New's child becomes ill and she cannot travel to an important cardiology meeting, she sees no alternative but to ask Dr Key to present her abstract for her. He has contributed little to this project but his name. After the meeting, a close associate reports to Dr New that Dr Key not only exaggerated his contribution, but also made discrediting statements about her methods. A few days later, another friend hears Dr Key commenting to the head of the Departmental Promotions Committee, "You can't really expect a young mother to stay at the top of the game."

Dr New drops by Dr Key's office and confronts him about his hostility. He demands to know the names of the "rumor spreaders" and denies any misstatements.

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TABLE 1.—*Women in Major Clinical Departments*

Department	1993 Residents %	1994 Faculty %	1994 Full Professors No.	(%)
Pediatrics	60	38	289	17
Psychiatry	43*	31	137	12
Family practice	39	31	31	11
Obstetrics/gynecology	53	33	53	8
Anesthesiology	23	25	40	8
Radiology	27	20	88	7*
Internal medicine	31	21	261	6
Surgery	17	10	54	3

*Do not represent increases from 1992.

Because it is now clear to Dr New that Dr Key has been deliberately trying to undermine her, she goes to see Dr Fair, the division chief who recruited her and continues to be her advocate. Early in her meeting with Dr Fair, however, Dr New uses the term "sexual harassment," and he does not let her finish. He says, "I never thought I would hear any women's lib stuff from you. You are both highly intelligent adults, and I trust you can work it out between you." His phone conveniently rings, and he dismisses her with a paternalistic pat on the shoulder.

A Year Later

Dr New smiles less often now and has no time for hallway conversation. She has taken on time-consuming committee work but still religiously protects her weekends for her family, so that she has fallen behind on getting her papers written and published. She will not have the requisite number of publications by the tenure review deadline. Dr Fair has left Prestigious for a job at Superlative Hospital. Dr Key has become division chief and interim chair.

Cumulative Disadvantages

The concept of cumulative advantages or disadvantages provides a useful framework for considering the whole range of sex differences in career development. Some advantages such as supportive parents or disadvantages like a history of clinical depression are relatively gender neutral. Men do, however, start out with some rarely mentioned advantages over women: they grow up seeing hundreds of examples of men who have changed history, made laws, and led countries and in a culture that expects and supports men's career ambitions. A discussion of disadvantages affecting the careers of women could begin in elementary school with evidence that girls are shortchanged compared with boys[5] and that adults tend to reward girls for politeness and boys for winning.[6] I will restrict my focus to problems that occur later in life.

As Dr New's case illustrates, although the success of many junior women faculty may look assured, often it is not, and not because of a lack of credentials or ambition. Many persons choose not to put career advancement first. The concern here, however, is assuring that the academic and practice environments be as free as possible of sex discrimination and that women have equal access to resources and to professional development opportunities.

Sexism

Although the main problem in the example is with one person, women more often experience sexism as a delegitimizing force in multiple but more subtle ways. Rowe coined the term "microinequities" to describe aspects of the work environment that are legally nonactionable and that may even escape conscious attention, but that are inappropriate, unfair, painful, and destructive.[7] Lenhart and Evans have documented a broad range of such microinequities—from deliberate exploitation to unconscious slights—that interfere with the professional development of women physicians and exact costly tolls on their self-confidence and relationships.[8] These oxymorons illustrate how slippery such microinequities can be: supportive discouragement, friendly harassment, radiant devaluation, benevolent exploitation, considerate domination, collegial exclusion.[9]

Collegial exclusion: Dr Key fails to invite Dr New to lunch with the group. *Supportive discouragement:* A department chair advises a new faculty member, "You are such an excellent clinician and teacher, you belong on the clinical track" (without exploring with her her research interests or the tenure track option). *Radiant devaluation:* A surgery professor says to a medical student, "You're much too pretty to become a surgeon." *Friendly harassment:* The department chair phones a faculty member at home two weeks after delivery of a child and opens the conversation, "So I've caught you at home goofing off." Such disparaging jibes present a thorny challenge. However fatigued this new mother may be, she is probably already feeling torn between the hospital and her child, so even if the remark was simply thoughtless rather than intentionally demeaning, it hits close to home. If she simply ignores the remark (as Dr New did), she invites further similar challenges. If she reveals any anger, she is open to accusations of "overreacting" or of not being able to "take a joke." Optimally, she would respond with a humorous retort that both "adequately disguises" her anger[10] and earns his respect and educates him about the inappropriateness of his comment. But this combination spontaneously delivered remains an unattainable feat for most women.

Such microinequities and communications difficulties can be imagined as a "ton of feathers"—cumulative in effect but far too subtle to be dealt with by policies or edicts.[11] Moreover, powerful persons may speak demeaningly to men and women alike, removing the issue from the realm of sex discrimination, even though young women seem more vulnerable to the adverse effects of verbal harassment. But academic medicine is no place for belittling comments directed at anyone, however ubiquitous they may sometimes seem. On an immediate and practical level, in our illustrative case it is clear that Dr Fair is ignorant of the law: managers can now be

held liable if it is shown they did not respond to employees' reports of sexual harassment. Further, the Supreme Court has ruled that women no longer have to prove psychological damage for sexual harassment claims to be actionable.[12] But while Dr New might be able to win a sexual harassment case, the act of filing would alienate enough people to destroy her academic career.

A final and particularly elusive aspect of sexism is the "comfort level," an important factor in selecting candidates for senior jobs.[13] So long as a culture's leadership continues to be dominantly male, women with qualifications equivalent to men candidates' will continue to be viewed as "risky" and penalized because they do not look or sound like the traditional chief executive. When a woman is hired, some will assume that the standards were lowered to achieve affirmative action; even when she appears to have broad support, she is still apt to be viewed as a token, with each move dissected in a search for weak points. Kanter labeled a group as "uniform" when composed mainly of one social type and "skewed" when including 20% or less of persons from another type, such as women.[14] In skewed groups, not only do tokens lack clout, they also face numerous loyalty tests, and any discrepant characteristics receive undue attention. Exacerbating the effects of these dynamics, many women remain uncomfortable with self-promotion because of their socialization and lack of mentoring.

Lack of Mentoring

Key to a successful career is a mentor, someone who acts as a guide and advocate with regard to resources and who enduringly cares about a protégé's advancement. Because of the large number of junior faculty and because most senior faculty seem always to be pressed for time, young men as well as women students and faculty may be hard pressed to secure a mentor. Because society comparatively undervalues women's careers, women's need for mentors to help identify strengths and resources may actually be greater than men's. Women have tended to underuse relationships at work that can help them advance, however, and the reasons for this are complex.

All women in positions of power have had excellent male mentors; mixed-sex mentorships can be challenging, however. Some men understandably perceive that a close relationship with a woman at work may be misinterpreted and are reluctant to mentor a woman or will be less forthcoming with a woman than with male protégés. Psychosexual insecurity can subconsciously get in the way as well. If a woman does not signal any sexual attraction, a man may feel personally rejected; on the other hand, if a woman does so signal, a man may think she is using her sex for professional gain. Thus, real or imagined sexual tensions can get in the way. Another difficulty is that because our society allows women a narrower range of assertive behavior than it does men, if a woman does not automatically accept what a mentor proposes, this may be considered an affront rather than a legitimate challenge.[15] Concomitantly, women seem to have more difficulty than men in separating from a mentor when necessary, in part because women sometimes become a mentor's "nurturer" or because the mentor may be jealous of others' attentions to his protégé.

Because women's developmental stages tend to be more complex and diverse than men's,[16] many women are looking for a different model of the mentor relationship than can be provided by senior men who have limited experience with protégés who have loyalties divided between career and family. Thus, it is not surprising that many young women would prefer a woman mentor. Nationally there are only about 13 women full professors per medical school, however, and that average includes basic scientists and nontenured clinical professors.

Unmentored or undermentored faculty are unlikely to think strategically about their career development. For instance, assuming that hard work will translate into just rewards, during job interviews faculty may leave to chance a discussion of salary and advancement options. Without a mentor, faculty seem less likely to come to understand key features of the organizational culture, to build effective informal networks, or to negotiate protected time and appropriate personnel and space. Sometimes, naive and unmentored faculty virtually waste the first few years of their appointment.

Structural Inflexibilities

The final category of disadvantages pertains to structural inflexibilities. As *Science* editor Donald Koshland stated: "A biologic clock that requires women to make a decision about a family in the same years that their commitment to research must be strongest makes pursuit of an academic career difficult. . . . Professional societies and academia have a responsibility to ease the burden on women during this critical period."[17(p1326)]

In an editorial titled "Here Come the Couples," it was noted that with 60% of women academic physicians married to other physicians: "Medicine will have to change its institutions. The old way of demanding single-minded dedication to medicine needs to be recast because it depended on a full-time backup for the rest of life's activities."[18(p630)]

As it is, tenure and promotion policies are geared to a 60- to 70-hour week, heavily favoring persons with few other responsibilities. And those who are shouldering family responsibilities have available to them few leave or reduced-schedule options. Only 34% of medical schools have specific policies for maternity leave that go beyond categorizing it as a form of disability leave, and only 18% have child care facilities.[19] A national study of part-time faculty in internal medicine found that almost half had developed the position themselves, and many reported difficulties related to lack of fringe benefits and promotion options and to negative attitudes of colleagues.[20] At most schools, faculty who wish to take off more than a month or two—and who can afford to—must take leave without pay, which may involve a suspension of benefits. Beyond that, a reduction of hours from anything less than full time usually means a part-

time position, even though for only half the salary the person might still work more than 35 hours per week. In most cases, this means being without benefits and forfeiting eligibility for committee memberships or promotions. At most schools, tenure track faculty choosing to reduce their hours even temporarily must drop off this track with little chance of reinstatement.

While there are some financial implications to offering expanded leave and reduced-schedule options, a more intractable barrier to creating flexible personnel policies is the sanctity in medicine of the full-time ethos: anyone who is working less than full time is suspected of lacking commitment and is written off. Such rationales go hand in hand with the unofficial and unhealthy precept that "good" physicians do not acknowledge personal needs.

Improving the Gender Climate

Because they may well be labeled as whiners and troublemakers, untenured women cannot speak about or point out examples of sex bias without the risk of damaging their careers. The leadership of men is therefore necessary in creating a forum to bring men and women together to discuss sexual stereotypes and bias. For example, Georgetown University (Washington, DC) School of Medicine's second-year bioethics course has included presentations on sexism as a moral issue and small-group discussions of a student case of sex discrimination. A required course such as this, legitimizing and encouraging the discussion of sensitive gender-bias issues, can open up consideration of other forms of bias and stereotypes. Grand rounds devoted to sexism and to women's professional development represent an even more valuable forum because most faculty and residents attend in addition to students.

A more comprehensive and targeted approach to improving the climate for women is in evidence in the Department of Internal Medicine at Johns Hopkins University (Baltimore, Maryland) School of Medicine.[21] With the support of an active group of women faculty, the department chair surveyed all departmental faculty and learned of specific gender problems that would have to be addressed if the department is to recruit and retain the best faculty. Next he appointed a task force and discussed survey results with all division directors, faculty, and residents. A consultant held workshops on eradicating gender bias with small groups of faculty and all division directors, and an office of faculty and organizational development was established.

Examples of other visible efforts to improve the environment for women are Yale University (New Haven, Connecticut) School of Medicine's Office for Women in Medicine, Stanford (California) University School of Medicine's dean's office requiring gender sensitivity training for all chairs and chiefs, and University of California, San Francisco, School of Medicine's appointment of an Associate Dean for Women.[22] A number of other schools have surveyed faculty and students to ascertain perceptions of sex discrimination and identify those areas most in need of addressing. One example of a smaller scale but promising activity is to include "preventive" discussions of gender bias issues in student orientation. The Association of American Medical Colleges' Women Liaison Officer network encourages the sharing of such information about successful strategies and programs, and *Building a Stronger Women's Program: Enhancing the Educational and Professional Environment* describes many such programs in detail.[22] A key factor in the enduring success of any work to improve the climate for women is a dean who sends clear messages about the unacceptability of sexism and who backs up words with actions.

Providing Skill Development Opportunities

Most continuing medical education courses address clinical skills, and most faculty development opportunities offered by medical schools focus on teaching skills. Given the demands of an academic career and the lack of mentors, many faculty also need assistance building a raft of other skills if their careers are to thrive: negotiating for resources, managing finances, promoting self, building informal networks, writing for professional journals, procuring grants, building a research program, managing conflicts, managing time, and balancing career and family. The American Association of Medical College's professional development seminars for junior and senior women faculty, devoted to these and related areas, were the first of their kind and continue to be oversubscribed. In addition to building skills, these seminars also stimulate exponential growth in participants' support and information networks and can be considered mentor-replacement therapy. Many medical schools have begun offering professional development workshops, sometimes open to men as well as women faculty.[22] Some specialty organizations also sponsor skill development opportunities geared especially to women. These vary in goals, length, organization, site, and expense, but such programs fill crucial gaps in the women's knowledge and provide them with sources of support they never knew existed.

Adding Flexibility

A few schools are also showing leadership in providing better options for faculty wishing to reduce their hours. In 1985 the Division of General Internal Medicine at the Medical College of Wisconsin (Milwaukee) created its "full professional effort" classification, meaning that all of a faculty member's professional effort is under the college's auspices, and since then not one of these faculty has left.[23] These faculty work at least half-time or more than 1,000 hours a year; malpractice coverage is paid, as are prorated vacation, sick leave, and retirement. Another innovation is that guidelines have been written for the promotion of these faculty on the clinician-educator track. Yale University School of Medicine allows tenure track faculty to work less than 100%, extending its usual 10-year probationary period to 13 years; the University of Pennsylvania

(Philadelphia) School of Medicine allows a similar extension.[24] The addition of such options builds loyalty and enhances the retention of committed faculty, likely offsetting any associated costs.

As the stereotype of the always-on-call, 60-hour-a-week physician alters to reflect new realities,[25] such accommodations will become more common in medicine, as they are in corporations endeavoring to keep and develop their best employees. As Koshland concludes: "Many women have accomplished the Herculean task of bringing up children and building reputations as very successful scientists, but the obstacle course they face is unfair to them and disadvantageous to society."[26(p1355)]

Conclusion

"Permanent white water"[27] vividly describes the environment in medicine for the foreseeable future—that is, volatile markets, new restrictions, unprecedented competition, and uncertainty regarding the shape and implications of health care reform. To compete, medical centers cannot afford to waste talent, especially of physicians dedicated to empathic high-quality patient care and those able to be superb role models. Yet, the talents of many young women faculty continue to be drained away by addressable disadvantages. Can Dr New's academic career be saved? Although her immediate prospects and environment are far from good, she might consider a number of options:

- Contact the American Cardiology Association's Committee on Women in Cardiology and start searching for a new mentor in her specialty and for other job possibilities—there are now almost 30 such women's specialty organizations or committees.
- Join the women faculty organization at Prestigious and take advantage of its information and support network. If none exists at the medical school, the university may have such an organization, or there may be a local chapter of the American Medical Women's Association. Find out how other tenure track faculty at Prestigious may have managed to obtain extensions to the probationary period.
- Enroll in a negotiating skills or conflict management workshop and practice confronting Dr Key until she is confident enough to do so effectively. Even though the climate in many places may still leave much to be desired from the point of view of a young woman faculty member, the only complete dead end is to assume the role of a victim. A future-oriented institution, however, will provide a favorable environment. A study on increasing the participation of women in physics found that the following factors are key: the commitment of the department chair, the presence of more than one senior woman faculty member, availability of day care, and a safe environment.[28]

Every medical center has within its power the ability to create scenarios for success, thereby assuring the recruitment and retention of the best faculty, many of whom will be women.

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Editorials

Treating Obstructive Sleep Apnea Syndrome—A Complex Task

CONGRESS MANDATED the establishment of the National Commission on Sleep Disorders Research in 1988. This action reflected the growing national perception that health problems exacerbated by sleep or caused by disorders of sleep represented an important public health issue. The commission concluded that approximately 40 million Americans suffer from chronic disorders of sleep and wakefulness, such as narcolepsy, obstructive sleep apnea syndrome (OSAS), and insomnia. It estimated that in 1990 sleep disorders and sleepiness cost the United States a minimum of $15.9 billion in direct costs alone. This estimate did not include the billions of dollars in indirect and related costs, such as those attributable to sleep-related tragedies like the *Exxon Valdez* grounding and space shuttle *Challenger* disaster.[1] As a result of the commission's findings, the National Center on Sleep Disorders Research was established in 1993 within the National Heart, Lung and Blood Institute of the National Institutes of Health.

Obstructive sleep apnea represents the second most common sleep disorder, insomnia being the most common. Estimated to affect about 20 million Americans, OSAS is associated with high blood pressure, coronary heart disease, heart attack, pulmonary hypertension, congestive heart failure, and stroke. While there are numerous reports in the literature suggesting markedly increased mortality from OSAS, generally from cardiovascular disease, adequate prospective studies need to be done to quantify the specific mortality of this disorder. Each year OSAS accounts for about $42 million in hospital bills, and the costs for the diagnosis and treatment of this sleep disorder could reach $60 billion by the year 2000.[2,3] In addition to its cardiovascular sequelae, OSAS results in excessive daytime sleepiness and consequent professional, social, and emotional problems. Excessive sleepiness itself poses a direct threat to life in a society heavily dependent on high-speed motor vehicle transportation. Recognizing the possible risk of sleepy drivers on the road, the governor of New York State in 1993 established a task force to study the problem of sleepiness as a cause of highway crashes. A survey of New York State drivers by this task force revealed that one in four drivers reported having fallen asleep at the wheel. A similar proportion reported knowing someone who had a crash resulting from having fallen asleep at the wheel. It was documented that, over a period of several years, half of the fatal crashes on the New York State Thruway were caused by sleepy drivers.[4] Drivers with OSAS may have seven times as many motor vehicle crashes as a control group.[5] Therefore, current understanding of the effect of OSAS on patients and society certainly justifies efforts to seek an effective protocol for treating this disorder.

The specific pathophysiologic basis for OSAS varies to some degree from patient to patient. The disorder reflects alterations in the respiratory control that is intrinsic to the sleeping state. It may be that in some patients the state-specific alteration in ventilatory control is abnormally pronounced and represents the primary cause of OSAS. In most cases, however, the immediate problem appears to be one of inadequate or disproportionate upper airway anatomy. In essence, the diminished dimensions or unfavorable configuration of the pharynx results in airway collapse during inspiration, when the protecting muscles assume their sleep-related decreased level of activity. The compromised anatomy results from the soft tissue structures that make up the pharynx and the underlying craniofacial skeleton that suspends the pharynx and determines its overall configuration. As persons gain weight, extra adipose tissue tends to compromise airway adequacy. The degree of obesity required before OSAS is established varies inversely with the degree of intrinsic inadequacy of a person's pharyngeal anatomy. The pharyngeal airway is a complex structure, and different sites within it may represent the region(s) of greatest vulnerability to collapse in different patients. Furthermore, although a given patient may have only one focus of narrowing and possible collapse, several such foci commonly exist.[6]

The treatment of OSAS is a complex undertaking. When obesity is a contributing factor, reducing weight may eliminate the OSAS or merely ameliorate it, depending on what factors other than obesity are present. The long-term loss of large quantities of excess weight by dietary measures alone is usually unsuccessful.[7,8] Nonetheless, weight reduction remains the first line of defense in an obese patient with OSAS. Various surgical approaches to weight reduction by physiologic malnutrition, such as gastroplasty and gastric bypass, have been used in treating morbidly obese patients with sleep apnea, with varying degrees of success.[9,10] The ultimate postoperative weight, which is usually reached after an initial period of weight loss followed by a period of weight gain, often represents a substantial decrease from the original weight, though not to a normal level. In some cases, this may be adequate for pronounced amelioration or resolution of OSAS. In other cases, substantial apnea may persist. Long-term follow-up of morbidly obese patients who have had a bariatric operation for OSAS is limited, and the degree of long-term benefit has not been adequately documented.

Attempts to treat the disorder with medication have met with little success, and this form of therapy rarely proves adequate.[11,12]

Devices resembling orthodontic splints are sometimes applied in the treatment of OSAS. Their goal is to prevent airway collapse in sleep by altering the position of the jaws and soft tissue components of the pharynx. The response to this treatment is variable and frequently

represents amelioration rather than elimination of the apnea.[13,14] There is little long-term follow-up data of effectiveness and patient compliance, and further studies are required.

Nasal continuous positive airway pressure (CPAP), a device that elevates the pharyngeal airway pressure and thereby prevents pharyngeal collapse, is almost universally effective when applied to patients in a sleep laboratory. It has for many years been regarded as the treatment of choice. There appears, however, to be a major problem with patient compliance. This was not documented until recently, when technologic advances permitted covert monitoring of patient CPAP compliance. It documented a great discrepancy between patients' subjective claims of use and actual levels of use.[15] Advances in technology will attempt to alter these devices to increase patient tolerance.

The surgical approach applied by the Stanford group has actually evolved over many years, as previous surgical attempts to treat OSAS fell short of the mark. Applying such traditional otolaryngologic approaches as nasal operation and tonsillectomy generally had only limited effects. Tracheostomy, though universally effective and for many years thought to be the preferred treatment of OSAS, had substantial limitations because of resulting psychosocial and physical drawbacks for patients. Uvulopalatopharyngoplasty, introduced in 1981, represented a major step forward in that it was the first surgical procedure specifically designed to treat the "disproportionate anatomy" of the pharyngeal airway in OSAS.[16] Whereas some patients were cured by the procedure, most had only amelioration of their OSAS. The problem appears to be that uvulopalatopharyngoplasty addressed only a limited portion of the pharyngeal anatomy. The site of anatomical compromise in a given patient may be at another portion of the pharynx, or there may be multiple sites. It has long been recognized that some patients with severe mandibular deficiency had OSAS on this skeletal basis, the posterior location of the tongue resulting in its tendency to fall back and occlude the pharyngeal airway in sleep. Such cases were effectively treated with surgical advancement of the mandible. The problem with this approach was that the vast majority of OSAS patients did not have the degree of mandibular deficiency, dental malocclusion, or both, that would permit this type of operation. Some patients who did meet the criteria for mandibular advancement had sites of pharyngeal obstruction in addition to the retrolingual one and therefore had only limited benefit from the mandibular advancement.

The work described by the Stanford group elsewhere in this issue represents a major advance in that it presents a conservative but comprehensive treatment protocol that aims for cure.[17] It combines nonsurgical therapy, traditional surgical approaches, and new innovative surgical procedures that are modifications of classic ones. The modifications were introduced by Riley and Powell to permit the application of procedures that did not otherwise meet the needs of most OSAS patients. The strength of the Stanford approach, which represents the state of the art, derives from many of its features: it is based on the premise that surgical intervention should be considered the preferred approach only when appropriate nonsurgical approaches have been presented, tried, failed, or were rejected by the patient. It approaches OSAS as a multifactorial disorder whose pharyngeal anatomical component is complex and may consist of multiple sites; techniques to define the anatomical abnormality or abnormalities are applied preoperatively to select a site-specific surgical approach; each site of pharyngeal compromise is considered in the surgical plan; the surgical approach includes modifying the soft tissue structures and the skeletal components, singly or together, as deemed necessary. It modifies classic maxillofacial surgical approaches, making them applicable despite the lack of major skeletal deficiency and malocclusion in most OSAS patients; the operation is carried out in a staged fashion, with relatively simple procedures grouped together as the first stage, and more complex procedures planned as a second stage only if necessary. Failure of the first stage, documented objectively by overnight polysomnography six months postoperatively, is the indication for considering doing the second stage. More than half the patients are spared the necessity of the second stage, as the first stage proves adequate to eliminate OSAS in that group. Therefore, the amount of surgical intervention is kept to a minimum; the goal is cure by contemporary concepts of what constitutes cure. The likelihood of achieving cure appears to be extremely high if those patients who require both surgical stages are willing to follow through with the entire surgical protocol; morbidity is modest, and there has been no mortality.

This protocol will need to be tested in the hands of other surgical teams. To date, only limited data of this type are available.[18,19] The application of more sophisticated techniques to identify the site(s) of pharyngeal abnormality might, if clinically practical, enhance the protocol. More extensive and comprehensive long-term monitoring of postoperative patients will be necessary to document the long-term efficacy of the approach.

The excellent results presented by the Stanford group demonstrate the importance of a surgical arm in the overall treatment protocol for OSAS. The etiologic complexity of OSAS, the broad range of severity of the disorder, and the interrelating interdisciplinary approaches to its treatment present a special challenge if patients with OSAS are going to receive optimal and cost-effective treatment. A similar challenge is faced by those who treat children with complex craniofacial disorders. Some institutions have responded to the challenge by establishing multidisciplinary craniofacial disorders teams based at comprehensive centers.[20,21] In such centers, the diverse specialists involved in all aspects of patient care form a team coordinated by a team leader. The team leader coordinates patient evaluation and treatment. The relevant medical specialists are involved simultaneously, or sequentially at the appropriate time, affording them

the opportunity to interact and bring their special knowledge and abilities into an integrated game plan for the advantage of each patient.

This approach can result in improved care, possibly at diminished cost, by permitting the development of comprehensive, integrated, patient-specific treatment plans that cut across the different disciplines involved. A goal is to eliminate redundancy of treatment and thus avoid patient frustration and needless dissipation of funds. The team and center can function in a research and educational capacity by building a database of the success and failure of specific simple and complex treatment protocols applied to different classes of patients. The treatment of OSAS appears to have reached the level of complexity where the team approach might be considered.

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Severe Mycoplasma Disease—Rare or Underdiagnosed?

PNEUMONIA IS one of the most common causes of morbidity and mortality in all age groups, but particularly in the very young and the very old. Yet, the causal agent remains unidentified in as many as 50% of cases. *Mycoplasma pneumoniae* is among the smallest free-living microorganisms, being intermediate in size between bacteria and viruses.[1] Its small genome and small size cause diagnostic difficulties. The organism is not visible on Gram's stains and does not grow on standard bacteriologic media. Even on specialized media, it can require as long as two to three weeks for growth and positive identification. More rapid antigen detection assays and the detection of nucleic acid by polymerase chain reaction appear promising, but still require serologic proof of current infection. Thus, most clinical laboratories and physicians' offices do not have the capability to diagnose this infection on a routine basis.

Because of diagnostic difficulties, the diagnosis of *M pneumoniae* infection is often based on excluding other agents. This has resulted in our lack of understanding of the disease-producing potential of this organism and perhaps its underdiagnosis in various patient populations. Based on recent studies using multiple diagnostic techniques, our concept of *M pneumoniae* respiratory disease is changing. *M pneumoniae* was previously thought to occur primarily in persons 6 to 21 years of age. Consequently, *M pneumoniae* was often not considered in the differential diagnosis of pneumonia in other age groups. This organism was thought to cause only a mild respiratory disease, so that it was not considered in the differential diagnosis in persons with severe pneumonia, particularly those who were admitted to a hospital or those who died. Extrapulmonary manifestations were reported in association with *M pneumoniae* respiratory infection almost half a century ago, but because of diagnostic difficulties the etiologic importance of *M pneumoniae* in these conditions was doubted.

Based on cultural isolation directly from the affected site, in combination with one or more additional diagnostic tests, there can no longer be doubt that *M pneumoniae* causes pneumonia in all age groups that can be fatal and that in some persons this same organism has the ability to produce invasive infection resulting in protean clinical manifestations. The cases reviewed by Chan and Welsh elsewhere in this issue of the journal are good examples and emphasize the need for further studies of this common respiratory pathogen.[2]

Mycoplasma pneumoniae *as a Cause of Disease in All Age Groups*

Current evidence indicates an infection rate of about 20% to 30% per year for *M pneumoniae*. The incidence rate is highest among schoolchildren and second highest among children younger than 5 years.[3] This organism was previously thought to be rare among children younger than 5 years and was thought to cause only acute, self-limited respiratory tract disease. Recent studies indicate that the peak age incidence may actually be highest among 3- and 4-year-old children and that there is a high rate of admission to hospital for *M pneumoniae* pneumonia among children younger than 5.[3,4] The popular belief that *M pneumoniae* disease is rare in this age group has precluded physicians from even considering it in the differential diagnosis.

One of the most comprehensive studies of the cause of severe respiratory disease in children was done by Kok.[5] Bacterial, mycoplasmal, and viral cultures plus serologic studies were done on 1,600 children younger than 15 years who were admitted to a hospital with severe respiratory disease. Overall, 6% of the cases were culture-positive for *M pneumoniae*, and of these, more than half were younger than 5 years. Of all *M pneumoniae* organisms identified, 20% were from children younger than 1 year. Of patients in whom *M pneumoniae* was identified, 72% were suffering from pneumonia, whereas the remaining 28% (18 of 64) of isolates were from patients with croup, bronchiolitis, or upper respiratory tract symptoms. The reverse was the case for those with evidence of viral infection: 64% of these had croup, bronchiolitis, or bronchitis, with the rest having evidence of pneumonia. In a prospective study of children admitted to the hospital for radiologically confirmed community-acquired pneumonia in Finland,[6] *M pneumoniae* was found to be the causative agent in 20%.

Recent studies in patients with a mean age of 62 years indicate that *M pneumoniae* also accounts for as many as 15% of cases of community-acquired pneumonia in this age group.[7,8] Prospective studies of adults (mean age, 56 years) admitted to a hospital with community-acquired pneumonia have confirmed that as many as 18% of cases are caused by *M pneumoniae*.[9] Thus, current evidence indicates that *M pneumoniae* should be considered in the differential diagnosis of pneumonia in all age groups, including patients with more severe disease.

Fulminant Pneumonia

Although severe mycoplasmal respiratory disease has been thought to be uncommon, recent reports, including the cases summarized in this issue of the journal,[2] suggest that the disease spectrum is wider than previously thought and that severe pulmonary involvement can occur in otherwise healthy children and adults of all ages. Because of the failure to routinely include *M pneumoniae* in the differential diagnosis of fulminant pneumonia, the exact frequency with which it occurs is unknown. The severe disease, often mimicking necrotizing bacterial pneumonia, can initially cause diagnostic confusion and therapeutic anxiety. Lung abscesses, Swyer-James syndrome, pneumatoceles, extensive lobar consolidation, respiratory distress, and pleural effusion may occur.[10] Although pleural effusion was formerly thought to be so rare in mycoplasmal infection that it suggested a different diagnosis, small effusions can be demonstrated in at least 20% of patients with the use of lateral decubitus chest roentgenograms.[11,12] *Mycoplasma pneumoniae* can be isolated from the pleural fluid in more severe cases.[12,13] *M pneumoniae* has been associated with exacerbations of chronic respiratory disease, in particular, chronic bronchitis and asthma,[10] but the role of this organism in sustaining the chronic state or in initiating exacerbation is unknown. The proven role of mycoplasmas in similar chronic diseases of numerous animal species,[1] however, suggests that careful, systematic studies should be undertaken. As indicated in the cases summarized by Chan and Welsh, anecdotal evidence suggests that the administration of corticosteroids may be useful in the treatment of severe cases of *M pneumoniae* infection.[2] Controlled treatment trials are critically needed, however. Whereas pulmonary lesions may appear less severe in immunocompromised persons and in animals, disseminated mycoplasmal infections involving multiple organ systems are much more prone to develop in these persons.[14]

Extrapulmonary Complications

Although a number of nonpulmonary complications occur in association with *M pneumoniae* infection, their exact incidence, pathogenesis, and clinical spectrum are unknown.

Central nervous system (CNS) complications were described in the initial report of primary atypical pneumonia in 1938, but because the cause of the respiratory condition was not yet known to be *M pneumoniae*, little could be deduced regarding the relation between the two. In the years that followed, many additional reports appeared. Up until 1978 more than 87 cases had been described, and by 1981 an additional 50 had been reported.[10] Over the past decade, individual case reports continue to be published almost monthly. Yet, the precise incidence has not been determined. Meningoencephalitis, aseptic meningitis, brain-stem encephalitis, ascending paralysis (Guillain-Barré–like), and transverse myelitis have all been reported to occur as complications of *M pneumoniae* infection. Cerebral, cerebellar, spinal cord, and nerve root involvement have occurred in combination, resulting in acute psychosis, cerebellar ataxia, and cranial nerve palsies.

Recovery from neurologic dysfunction has often been slow, requiring many months of hospital care. Some cases have been fatal (overall mortality, 10.3%), and about a third of the patients who have recovered have been left with a permanent or persistent neurologic deficit. Two of the seven patients with fatal nonrespiratory failure reviewed in this journal by Chan and Welsh had CNS involvement (meningoencephalitis and brain

edema in one and cerebritis, meningitis, and cerebrovascular thrombi in the other).[2]

Initial failure to show direct CNS invasion by mycoplasmas and the fact that many reported cases were based solely on serologic evidence led many investigators to regard the association of *M pneumoniae* infection and CNS disease as rather tenuous. As stated by one investigator,[15] when a disease is as common as *M pneumoniae*, it can be related by coincidence alone to many life events. Several factors suggest that the association may be more than tenuous, however. It has been estimated that 0.1% of all patients with *M pneumoniae* infection and 7% of those requiring admission to a hospital have CNS complications.[12,16] On the other hand, the incidence of *M pneumoniae* infections among patients with acute, febrile, nonbacterial affection of the CNS was shown to be 5%, with a maximum of 10% during an epidemic.[17] These figures are supported by the fact that in five succeeding years, a constant percentage (6.7%) of patients with *M pneumoniae* infection were shown to have CNS complications.[18] More than half the reported patients with CNS disease have been from 6 to 21 years of age—the age group most prone to have *M pneumoniae* respiratory disease. Support is also afforded by the similar distribution, both seasonal and annual, of the patients with CNS symptoms and other manifestations associated with serologically verified *M pneumoniae* infection.[16]

The repeated occurrence of mycoplasmal pneumonia and encephalitis in immunocompetent persons suggests some as-yet-unexplained predisposition.[19] The absence of concomitant bacterial or viral pathogens was demonstrated in a number of patients with CNS disease,[15,20] whereas *M pneumoniae* infection was documented by a fourfold rise in the titer of complement-fixing antibody, the presence of typical respiratory symptoms, and the development of cold agglutinins. Diagnosing infection by a rise in complement-fixing antibody titer alone has been a cause for concern because the lipid antigen used in this test cross-reacts with certain lipid antigens in brain.[17] Findings in more than 1,000 patients with neurologic disease of other causes, however, suggest that nonspecific serologic cross-reactivity does not lead to an erroneous diagnosis of *M pneumoniae*-associated CNS disease.[12,18] More important, infection has been documented by cultural isolation of *M pneumoniae* from the cerebrospinal fluid and brain tissue at autopsy.[21-23] Thus, an association between CNS disease and *M pneumoniae* infection clearly exists, but further cultural and serologic studies are needed for a better understanding of their precise relation.

In 33% to 76% of patients, *M pneumoniae* infection evokes immunoglobulin M autoantibody that agglutinates human erythrocytes at 4°C (cold agglutinins). Positive Coombs' tests in 83% of patients and the presence of reticulocytosis in 61% suggest that subclinical anemia may be common.[11] Mycoplasmal organisms use specific long-chain sialo-oligosaccharides at the host cell surface as receptors. These sialo-oligosaccharides contain I antigen, and they are richly expressed at the primary site of infection—the ciliated bronchial epithelium—and on erythrocytes. The autoantibodies directed to I antigen, frequently produced in this infection, are antibodies to receptors and may be triggered by an autoimmunogenic mycoplasma-receptor complex in which the lipid-rich microorganism serves as an adjuvant.[24] Complications with or without the hemagglutination response include hemolytic anemia, paroxysmal cold hemoglobinuria, Raynaud's disease, peripheral symmetric gangrene, diffuse intravascular coagulation, thrombocytopenia, and renal failure.[11,16] Hemolytic anemia was a common finding in the fatal cases summarized by Chan and Welsh.[2]

Cardiac involvement in *M pneumoniae* infection is generally thought to be rare, but its actual incidence is unknown. The one prospective study reported shows that cardiac involvement may occur in as many as 4.5% of patients.[25] Myocardial dysfunction is often associated with hemolytic anemia and may mimic myocardial infarction.[26] Myopericarditis, hemopericardium, congestive heart failure, and complete block have been reported to occur.[12,16] The signs and symptoms of acute illness are variable, but may require intensive care with ventilatory assistance, temporary pacemakers, and defibrillation.[25] Cardiac sequelae have been known to persist for as long as 47 months.[27] In other patients, pronounced electrocardiographic changes reflecting myocarditis may be present without cardiac symptoms.[27] Myocarditis was present in several of the fulminant cases reviewed by Chan and Welsh.[2]

Although it is difficult to arrive at any definitive conclusions regarding cause and effect from published reports of myocardial involvement, the clinical presentations suggest an association with *M pneumoniae*. Cultures are negative for bacteria, and in most cases viral serologic tests are either negative or unchanged. *M pneumoniae* infection has been documented by a fourfold rise in antibody titer, elevated cold agglutinin levels, typical respiratory signs and symptoms, and direct isolation of *M pneumoniae* in pure culture from pericardial fluid and cardiac tissue.[11,28] In a prospective study of 57 patients with new, large pericardial effusions who underwent subxyphoid pericardiotomies, *M pneumoniae* was identified in pericardial tissue or fluid (or both) in 2.[29,30] No other cause of the pericarditis was identified in these two patients. Neither of the patients had pneumonia at the time, but one of them did have pleural effusion. Both were older than 60 years and had other underlying diseases.

Mucocutaneous lesions occur in approximately 25% of cases of serologically or culturally proved *M pneumoniae* infection.[11,12,31-33] Of these lesions, erythematous maculopapular and vesicular exanthems are most common. Half of these patients also have ulcerative stomatitis and conjunctivitis—Stevens-Johnson syndrome. Although the cause of this disease appears to be complex, more than 20 cases have been well documented to have *M pneumoniae* infection.[11,31,34,35] In addition to serologic evidence of infection, many patients have had

throat cultures positive for *M pneumoniae* and positive bullae-fluid cultures.[31,36] It has been suggested that *M pneumoniae* infection simply intensifies the dermatosensitive potential of certain antibiotics, but the development of the Stevens-Johnson syndrome in patients before therapy supports the contention that exanthems can occur in the absence of antibiotic therapy.[31,34] Other skin lesions that also occur in association with *M pneumoniae* infection but that are not of major importance include macular, petechial, morbilliform, and papulovesicular rashes; scaly erythema; pityriasis rosea; erythema nodosum; varicella-like rashes; and urticaria.[31]

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Correspondence

More on Lovastatin

To the Editor: Von Pohle's letter "Recurrent Hyperthermia Due to Lovastatin" in the October issue[1] was interesting and informative. He makes a good case for lovastatin as a plausible cause for his patient's recurrent hyperthermia, as rechallenge with the drug produced identical symptoms. I wish to point out an underrecognized but potentially serious interaction between lovastatin and erythromycin, a combination that the patient in von Pohle's report was taking at the time of her initial presentation.

Lovastatin, an inhibitor of 3-hydroxymethyglutaryl coenzyme A (HMG-CoA) reductase, is a widely used drug in the treatment of hypercholesterolemia.[2,3] Side effects are usually minor and include asymptomatic elevated aminotransferase levels, skin rash, gastrointestinal disturbances, and skeletal muscle abnormalities, including asymptomatic elevations in creatine kinase levels, myalgias, weakness, and rhabdomyolysis.[2,4] The most clinically important adverse reaction is rhabdomyolysis accompanied by acute renal failure. Although lovastatin use by itself has been associated with rhabdomyolysis, most cases reported in the literature occurred in patients taking gemfibrozil, cyclosporine, or niacin.[2,5,6] Lovastatin is metabolized by hepatic microsomes, and notable interactions may occur when used in conjunction with other drugs that are metabolized in a similar manner.[3] There have been three cases of rhabdomyolysis—one of which was complicated by acute renal failure and death—that occurred after erythromycin was added to a stable regimen that included lovastatin.[2-4]

Erythromycin is a macrolide antibiotic that is metabolized in the liver by the cytochrome P-450 system, likely the same enzyme system responsible for metabolizing lovastatin.[6] Erythromycin inhibits the elimination of other drugs including theophylline, warfarin, and carbemazepine.[3] By possibly inhibiting the hepatic microsomal P-450 system, erythromycin may increase serum levels of lovastatin.[2,3] Furthermore, both erythromycin and lovastatin are highly bound by serum proteins, and the addition of erythromycin to lovastatin may raise serum levels of lovastatin by displacing the drug from protein-binding sites.[2,3,6] The reported cases of rhabdomyolysis attributed to lovastatin and erythromycin use document increases in serum lovastatin levels between 3 and 10 times the upper limits of normal after the addition of erythromycin.[2-4]

The pathophysiology of lovastatin-induced muscle injury is unknown. Higher than normal levels of lovastatin may alter the stability of skeletal muscle membranes, however, causing leaking of creatine kinase with the subsequent development of rhabdomyolysis.[4] Studies in animals of the effects of simvastatin and pravastatin, both HMG-CoA reductase inhibitors, have shown clinical signs and histopathologic evidence of skeletal muscle injury when high doses were used.[7]

Although only a few cases of erythromycin-lovastatin associated rhabdomyolyis have been reported, they document the importance of considering pharmacologic interactions when prescribing drugs that are metabolized in a similar manner. Given the widespread use of lovastatin and other HMG-CoA reductase inhibitors and the many indications for erythromycin and other newer macrolides, clinicians must be aware of the real possibility of rhabdomyolysis occurring if agents from these two classes are used concurrently. Because rhabdomyolysis can result in renal failure or even death, it may be prudent to discontinue lovastatin therapy temporarily if the clinical situation necessitates the use of erythromycin or other macrolides.

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Dr von Pohle Responds

To the Editor: Dr Marinella's comments are appreciated. He is correct to point out the association of erythromycin and 3-hydroxymethylglutaryl coenzyme A reductase inhibitors. Both agents are highly protein-bound and interact with multiple agents. As Dr Marinella notes, this patient was taking erythromycin and lovastatin at the time of the first admission. At the second admission she was receiving ofloxacin and lovastatin. Reported interactions of quinolones with agents that are metabolized by the cytochrome P-450 system are complex and variable.[1,2] Ciprofloxacin, perfloxacin, and enoxacin have a high inhibitory effect on the cytochrome P-450 system, while ofloxacin, fleroxacin, and temafloxacin have a low inhibitory effect. In addition, ofloxacin is almost entirely renally excreted, and its effect on theophylline concentration has been reported to be minimal.[3] It would seem unlikely that an ofloxacin and lovastatin interaction from inhibition of the cytochrome P-450 system would have produced this patient's symptoms.

A further interaction, not mentioned by Marinella, is that of lovastatin and thyroid replacement agents. Cases of both hypothyroidism and hyperthyroidism have been reported.[4,5] Another report states that in patients euthyroid on long-term replacement therapy, thyroxine concentrations were not affected.[6] The mechanism of interaction has not been established. At the time of the third admission our patient was euthyroid on replacement therapy and no other agents that would have affected the cytochrome P-450 system. It would seem unlikely based on reported data that this interaction was occurring in this patient. Cases of interaction with furosemide and levodopa-carbidopa, the additional medications this patient had taken, have not been reported. This again should alert clinicians to the increasingly complex pharmacodynamics of drug interactions and the increasing number of potential complications that can arise from treatment.

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A Patient's Paper Chase

To the Editor: A troubling feature of medicine in the United States is the excessive paperwork required of physicians. But what about the excessive paperwork of their patients?

Unlike many Americans, I have excellent medical insurance. I can, for example, consult any physician in the world. Yet, here is what happens whenever I become a patient: each physician bills Medicare and then waits to hear from my secondary and tertiary insurers; Medicare and the tertiary insurer pay quickly and directly. The secondary insurers do not. When I asked them to do so, they replied: "Two issues have influenced our decision not to. . . . The issuing of the [Internal Revenue Service] 1099 forms to out-of-state providers, along with the related record-keeping, was viewed as administratively costly. Secondly, our legal counsel had concerns about possible discrimination if we treated one group of providers [such as those in Pennsylvania] differently than another group [those out-of-state]." So none of my Oregon physicians or hospitals ever gets a penny from my secondary insurers. Instead, I get an "Explanation of Benefits" with either a check for full or partial payment or a reason why the insurer will not pay; if the check is for full payment, I send my own check to the physician, and the matter ends there. If I get partial or no payment, I photocopy the bills and explanations of benefits, fill out a form, and send all these papers to my tertiary carrier.

As a retired beneficiary of American capitalism, I believe in the primacy of the private sector. I do not believe, however, in the myths that business never does things wrong and government never does them right. Nor do I accept the notion that if we pay for something through taxation, it always costs more than if we pay for it through private purchase.

Although the overall cost of administering health care in the United States is 25%, in single-payer Canada it is 10%. And the 14% overhead of US insurance companies is more than three times that of our Medicare and Medicaid programs.

I have misgivings about US companies making so much profit from selling health insurance or from "managing" health care. I also share physicians' concerns about intrusions by nonmedical persons into decisions involving patient care.

Despite the current "Let's-get-the-government-off-our-backs" mood, I favor a federally run, nationally portable, geographically neutral, single-payer, free-choice-of-physician, solo-practitioner-friendly, fee-for-service, single-card, one-national-claim-form, little-or-no-patient-paperwork health insurance program for all citizens and permanent residents of the United States. And I suspect that most patients—in exchange for a slowing of their paper chase and the right to choose their own physicians again—would favor it, too.

I suspect as well that more physicians than we think—in exchange for reductions in paperwork, more freedom to make medical judgments, and an escape from the crushing constraints of insurance companies and managed care conglomerates—would also favor such a program today.

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Pregnant Teenagers

To the Editor: I found Bluestein and Starling's article on "Helping Pregnant Teenagers"[1] generally useful and accurate. There are, however, two points where I would expand on what they said. First, they place excessive emphasis on teenagers' "ambivalence about contraception." A more important problem is adults' and medical professionals' ambivalence about contraception for teenagers resulting in inadequate information about sexuality and contraception and a lack of access to services.

Second, I agree that a "newly pregnant teenager must decide whether to continue the pregnancy" and that "lack of information poses additional difficulties." But medical professionals have an obligation to go beyond stating that the "medical risks of first trimester terminations for teenagers are generally low." There is an additional obligation to explain the alternatives and their rel-

ative risks. Once pregnant, there are only two alternatives: continued pregnancy with childbirth, and termination of the pregnancy. Childbirth poses a 5-fold greater risk of death and a 200-fold greater risk of serious abdominal surgery than pregnancy termination. The raw statistic of a "teen mortality rate of 1.3 per 100,000 procedures" is meaningless to a teen or her partner or parent, except in comparison to the mortality rate of 7.9 per 100,000 for childbirth.[2] Likewise, a risk of emergency abdominal surgical procedures of "1 to 2 per 1,000 teenagers undergoing first-trimester abortions" should be compared with the 20% to 25% (200 to 250 per 1,000) rate of cesarean sections, which is the comparable "emergency abdominal surgical procedure" related to childbirth. Therefore, I show teens—and adults—who have ambivalent or adverse feelings about their pregnancies graphs that illustrate this information in an easily understandable form.

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REFERENCES

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* * *

Dr Bluestein Responds

To the Editor: Dr Ferguson raises important issues concerning the prevention of unintended pregnancy and informing pregnant teens about medical risks. I agree that the problem of unintended pregnancy is best managed by underutilized preventive strategies such as contraception. Unfortunately, this underutilization is more than a matter of unavailability or adverse social pressure, although these factors are both barriers. Most of the social and developmental issues affecting the use of maternal health services in pregnancy dictate contraceptive usage as well. Consequently family planning should be stressed in the preventive care of adolescents with the use of relationship-building strategies such as my coauthor and I describe. Further discussion of rapport building using patient-centered interviewing skills is presented by Stewart and Roter.[1] Their text points out that effective communication requires appreciating patients' values and perspectives, even when these differ from one's own. On the other hand, arguing for one's beliefs is appropriate in shaping organizational position statements.

Ferguson's second point concerning medical risks underscores the importance of effective patient education. Using a visual strategy such as a simple graph can help to simplify and dramatize information that might not otherwise be understood. I would suggest, however, that except for younger adolescents, the risks of childbearing can be reduced by prenatal care and health-protective behavior during pregnancy and beyond. It is important to share this information as well.

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REFERENCE

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Virginia

DONALD W. HASSEMER, MD, *San Juan Pueblo, New Mexico*

Virginia's first husband died when he was 36 and she was 31. She had two young boys to rear, so she married again, to a man much older—for "security." Working and rearing yet another son never seemed to age her. Her second husband died, and she eventually married a third time. I do not think she ever knew why she remarried, but I know she regretted it. Her older sons left home, and her third son's relationship with her husband brought nothing but turmoil and pain. She kept working and playing the peacemaker as best she could, but her son was destined not to have a father.

Her third husband died. She moved to Santa Fe, to get out of the cold and snow of Wisconsin and to be with her other sons. In 1982 she asked me, "What is this lump under my breast?"

"How long has it been there?" I asked.

"Four months," was her nonchalant reply. Two days later it was confirmed to be carcinoma, with positive axillary nodes. She underwent adjuvant radiotherapy, and three years of symptom-free living followed.

In 1986, when she was 65 years old, during a routine echocardiogram for a workup for uncontrolled hypertension, a pericardial effusion was discovered that proved to be malignant. Bone metastases were found in her vertebrae and ribs. She endured 18 months of chemotherapy—three days each time of nausea and vomiting, followed by three days of dread. Her only complaints were about the cost and the smaller clothing she needed because of her weight loss. Suddenly she seemed better. The chemotherapy stopped, and her activities returned to nearly normal. She volunteered at the Children's Museum and visited her family in Missouri, Wisconsin, and Florida. She took up tap dancing and, wearing a leotard and tights, performed routines with her newfound friends.

The most amazing observation about Virginia was her optimistic belief that she would not die of the "damned disease." When the estrogen blockers and the androgenic drugs stopped working and the disease progressed, she took it in stride, shaved her chin, and told jokes about it. She made cakes and cookies for her physician and his staff. Interstitial pulmonary spread of the cancer made her need oxygen even for the simplest household chores, yet she remained confident that she was not going to give in. When the visiting nurses came to express their concern that she needed to talk about death and dying, she tossed them out, knowing what was happening and not yielding to the temptation to give up. Through all of this, she trusted her oncologist without question, knowing that he was doing his best.

In December 1992, when she was 75, her sons and daughters-in-law gave her a birthday party at which she absolutely glowed. Friends and family from far away saw how, with resolution, grace, and dignity, she overcame pain. They saw how she overcame dread and pessimism to live with whatever she had to face.

At 75, Virginia died.

After being with this special patient for the ten years of her illness, I saw what physicians who care for seriously ill, even dying patients, rarely see. Virginia—my mother—was a woman with extraordinary strength, and yet each patient deals with their own mortality in uniquely adaptive ways. We cannot impose our own set of values on patients. If we do, we risk stifling the important yet very personal resolve to go on. Let us never underestimate the will to "go on living" as a powerful adjunct to our treatments. Listening can transform our interactions from mere caring to empowerment.

(Hassemer DW: Virginia. West J Med 1995; 162:179)

Dr Hassemer is a family physician in Española, New Mexico.
Reprint requests to Donald Hassemer, MD, Route 2 Box 285, San Juan Pueblo, NM 87566.

The Most Basic Need

CONNIE POSS, *Salt Lake City, Utah*

I stood silently in the entrance to the treatment area of the Emergency Department, not wanting to interrupt those at work inside. The errand that had brought me to this doorway had been simple: to retrieve an ID card from my husband's wallet and to borrow some cash. I left much richer that day, not from the money that I had tucked away in my pocket, but from what I had seen.

Like most of us, my husband has many jobs—husband, son, father, physician. I had been able to watch him at work as a husband for the past five years and savored the moments when I witnessed his skill at being father and playmate to our 2-year-old son, but I had rarely had the chance to see him in his job as healer. That day, leaning against the door frame, I was able to watch, undetected, and I began to understand why my husband loves his work.

He says that ever since he can remember, he wanted to be a pediatrician. He has always had a soft spot in his heart for the kids. Pleading temporary insanity, I married him the summer before he started medical school. Once we survived that period, we moved on to the challenge of residency, with challenge being the key word on many days. Long hours, sleepless nights, and shortened tempers led to a slight drop in his job performance ratings as husband and father, but his dedication to his role as physician never wavered.

That day I spotted him across the room, trying to gain the approval of a frightened little girl who was clinging furiously to her mother. When his first attempts at approaching her met with great resistance, he took off his coat and sat down on the shiny metal stool, slowly inching closer. I stood transfixed as I watched him slowly and patiently become her friend before he became her physician, his face softening as it became more obvious that he was succeeding in this important task. The smile on his face now was one somehow more genuine than the one that is a part of the uniform all physicians wear. He never made her sit on the examination table before she was ready, never told her that she had to sit still and behave, never lectured her about the importance of cooperation. First and foremost, he tried to make her feel comfortable and safe. Only then did he proceed with the examination.

I had seen the gentle, nurturing side of him at home, in the privacy of our own four walls, but it was refreshing to see that those characteristics carried over into all aspects of his life.

After finishing the examination he spent several minutes talking reassuringly to the little girl's anxious mother, allowing her also to feel comfortable and safe. He never rushed or acted as if he was hurrying off to his next patient, but, rather, remained there patiently answering questions and providing instructions. After gently lifting the girl from the table, he reached into his pocket and presented her with a tangible reward for trusting in him—a symbol of friendship, no strings attached. A smile covering her face from ear to ear, she grabbed his hand as they headed toward the door.

My few moments of being an undetected observer were over, but I felt fortunate that I had been able to see the gentler side of medicine, however brief it may have been. Standing there in that doorway, watching him work, I understood his dedication. I forgot about the long hours, the interrupted dinners, the calls in the middle of the night. This was what it was all about. He loved his work.

It is nice to know in this day and age of frantic pace, advanced technologies, and medical miracles, perhaps the secret to good medicine lies in the most basic need—a caring physician with a ready smile and a warm heart.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Poss C: The most basic need. West J Med 1995; 162:180)

Reprint requests to Connie Poss, 2850 Nora Dr, Salt Lake City, UT 84124.

(Continued from Page 114)

April 6-7—**Advanced Techniques in Angioplasty**. Cedars-Sinai Medical Center at Hotel Sofitel Ma Maison, Los Angeles. Thurs-Fri. 15.5 hrs. Contact: Bari Laner, Cedars-Sinai, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937

April 28-30—**Arrhythmias: Interpretation, Diagnosis and Management**. Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

May 11-13—**5th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12—**Stress Echo: Meet the Experts**. Hospital of the Good Samaritan. Fri. Contact: Charles Pollick, (213) 977-2335

CRITICAL CARE

March 13-17—**Critical Care Medicine.** USC at Caesars Palace, Las Vegas. Mon-Fri. 33 hrs. $595-$720. Contact: USC

DERMATOLOGY

June 9-11—**3rd Annual Skin Rejuvenation Seminar.** Medical Education Resources at Cosmetic Surgery Group of Newport Beach. Fri-Sun. 19 hrs. $2200. Contact: Martin Borsanyi, c/o The Professional Image, (714) 760-1522

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

February 19-24—**18th Annual Emergency Medicine: 1995.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. Contact: UCD

March 6-10—**15th Annual Mammoth Mountain Emergency Medicine Ski Conference**. American College of Emergency Physicians at Mammoth Lakes. Mon-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, P.O. Box 52-B, Newport Beach 92662. (714) 650-4156.

March 6-10, May 8-12—**Clinical Applications of Hyperbaric Oxygen** Therapy/Wound Care Management Courses. Long Beach Memorial Medical Centers. Mon-Fri. Contact: Celia Loney, LBMMC, PO Box 1428, Long Beach 90801-1428. (310) 933-6950.

March 13-17—**Critical Care and Emergency Medicine**. USC at Caesars Palace, Las Vegas, Nevada. Mon-Fri. 34.5 hrs. $595-$720. Contact: USC.

March 13-17—**Emergency Medicine Symposium**. UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 8-12—**Emergency Medicine Symposium I**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 16-17—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at San Francisco. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

June 19-23—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-21—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

EPIDEMIOLOGY/INFECTIOUS DISEASE

April 2-4—**5th Annual Meeting of the Society for Healthcare: Epidemiology of America.** UCSD at Town & Country, San Diego. Sun-Tues. 17 hrs. $435. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

March 29-31—**Annual Review in Family Medicine**. UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

March 30-April 1—**45th Yosemite Postgraduate Institute.** Fresno-Madera Medical Society at Yosemite National Park. Thurs-Sat. 12 hrs. $200-$250. Contact: Carol Rau, 3425 North First St, PO Box 31, Fresno 93707. (209) 224-4224.

April 10-13—**Primary Care in Paradise: Maui 1995.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21—**Preventive Health Screening in the Elderly**. UCD at Cancer Center Auditorium, Sacramento. 7 hrs. Contact: UCD.

April 27-30—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

May 10-13—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

May 20—**Gynecology for Primary Care**. UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. Contact: UCD.

July 10-13—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425. Contact: UCSF.

GERIATRICS

March 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims**. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

HEMATOLOGY

March 16-18—**Recent Advances in Hematopoietic Stem Cell Transplantation**. UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 30-April 1—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Thurs-Sat. 18 hrs. $500. Contact: UCSD.

INTERNAL MEDICINE

February 19-24—**Emergencies in Internal Medicine: 1995**. UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $495. Contact: UCD.

February 25—**Sjogren's Syndrome: A Symposium for Patients and Professionals.** USC at Louis B. Mayer Teaching Center, Los Angeles. Sat. 4.5 hrs. $85. Contact: USC.

March 3—**21st Annual Diabetes Symposium—Diabetes Control and Complications Trial: Implementation**. UCD at Holiday Inn Sacramento, North. Fri. 7 hrs. $130. Contact: UCD.

March 17-23—**Internal Medicine 1995: A Comprehensive Review.** Continuing Medical Education Associates at Hotel del Coronado. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-April 1—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Hapuna Prince Hotel, Kamuela, Hawaii. Sat-Sat. 29 hrs. $595. Contact: USC.

April 22-23—**Minimal Intervention in Vascular Disease.** Scripps Memorial Hospital and Scripps Clinic and Research Foundation at Hyatt Regency, San Diego. Sat-Sun. Contact: Laurel Steigerwald, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

February 18-24—**Perinatal Medicine.** USC at Westin Maui Hotel, Hawaii. Sat-Fri. 30 hrs. $595. Contact: USC.

ONCOLOGY

February 20-23—**Clinical Hematology and Oncology:** 1995. Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 28 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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March 11—**Challenges and Controversies in the Prevention and Management of Colorectal Cancer.** Saint Vincent Medical Center's Los Angeles Oncologic Institute. Sat. 3 hrs. Contact: Claudia Ostrum, Box 57992, 2131 West Third St, Los Angeles 90057-0992. (213) 484-7888.

April 10-14—**20th Annual Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

April 1—**Ophthalmology Laser Course**. UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. Contact: UCD.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

ORTHOPEDICS

May 18-21—**10th Annual Symposium of the Spine Study Group**. Spine Study Group at Westin Mission Hills, Rancho Mirage. Thurs-Sun. Contact: Pat Curl, Meeting Coordinator, 4805 Mercury St, Ste E, San Diego 92111. (619) 279-9955.

OTOLARYNGOLOGY

February 26-March 3, March 26-31—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach**. UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

PATHOLOGY

February 28-March 4—**Classical Morphologic Approaches and Newer Diagnostic Techniques to Blood Disorders.** American Society of Clinical Pathologists at Meridien Hotel in Coronado Island, San Diego. Tues-Sat. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612-3798. (800) 621-4142.

March 1-5—**34th Annual Convention and Scientific Exhibit Show of the Osteopathic Physicians and Surgeons of California**. American Osteopathic Society at Anaheim Hilton and Towers. Wed-Sun. 46 hrs. $495. Contact: Kimberley Bauer, OPSC, 455 Capitol Mall, Ste 230, Sacramento 95814. (916) 447-2004.

April 1—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 25-27—**Current Issues in Anatomic Pathology: 1995**. UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF

PEDIATRICS

February 20-22—**Pediatrics Update 1995.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 3-5—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. $365. Contact: Children's Hospital, 3020 Children's Way, San Diego 92123. (619) 576-4072.

March 10—**Causes and Treatment of Craniofacial Anomalies**. Cedars-Sinai Medical Center at Hotel Sofitel Ma Maison, Los Angeles. Fri. 7 hrs. Contact: Bari Laner, Cedars-Sinai, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937.

March 31-April 1—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center and UCSD at Hyatt Regency, La Jolla. Fri-Sat. 12.75 hrs. $245. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

May 4-6—**28th Annual Advances and Controversies in Clinical Pediatrics**. UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

July 21-22—**3rd Annual Pediatrics Update**. Stanford University at Lucile Packard Children's Hospital. Fri-Sat. Contact: Elinor Meyer, Continuing Medical Education, 725 Welch Road, Palo Alto 94304. (415) 497-8554.

PSYCHIATRY AND NEUROLOGY

February 23-26—**Breakthroughs in Psychiatry and the Law: Dangerousness and Its Discontents.** UCSD at La Jolla Marriott. Thurs-Sun. 15.5 hrs. $310. Contact: UCSD.

February 25-26—**You Will Learn Hypnosis: The Basic Skills.** Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $325. Contact: SCSCH, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

February 26—**Healing With Heart: Manifesting Magnificent Metaphors**. Southern California Society of Clinical Hypnosis at Airport Marina Hotel, Los Angeles. Sun. 6 hrs. $180. Contact: SCSCH, 10840 Queensland St, Los Angeles 90034. (310) 475-1260.

March 30-April 1—**Volcanoes and Tidal Waves: Contemporary Challenges in Psychiatry**. Hawaii Medical Association at Hilton Hawaiian Village, Honolulu. Thurs-Sat. 12 hrs. Contact: Jan Estioko, 1360 S Beretania St, 2nd Fl, Honolulu, HI 96814. (808) 536-7702.

March 31-April 2—**West Coast Psychiatry Board Review: Preparation for Part II**. UCSD at La Jolla Marriott. Fri-Sun. 16 hrs. $525. Contact: UCSD.

April 7-9—**West Coast Neuropsychology Conference: New Advances in the Assessment and Treatment of Cognitive Deficit in School-Age Children**. UCSD at Pan Pacific Hotel, San Diego. 14.5 hrs. $325. Contact: UCSD.

May 24-26—**14th Annual Child Abuse and Neglect Conference**. UCD at Red Lion Hotel, Sacramento. Wed-Fri. 15 hrs. Contact: UCD.

July 25-30—**Neuropsychiatric Emergencies and Crisis Update and Review**. Southern California Neuropsychiatric Institute at Mauna Kea, Hapuna Beach Hotel, Hawaii. Tues-Sun. Contact: Ann McCormick, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102

PULMONARY MEDICINE

March 23-29—**National Association of Medical Directors for Respiratory Care**. University of Nebraska Medical Center at Silverado Hotel, Napa Valley. Fri-Wed. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

RADIOLOGY

March 5-9—**Neuro and Musculoskeletal MR.** UCSD at Hotel Del Coronado, San Diego. Sun-Thurs. 30 hrs. $600. Contact: Dawne Ryals, Ryals & Associates, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 5-10—**General Radiology Review.** UCLA at Guest Quarters Suite Hotel, Santa Monica. 40 hrs. $420. Contact: UCLA.

March 5-10—**Magnetic Resonance Imaging of the Brain, Spine and Musculoskeletal System**. UCSD at Hotel del Coronado. Sun-Fri. 30 hrs. $625. Contact: UCSD.

March 10-12—**Musculoskeletal Imaging**. UCSD at Hotel del Coronado. Fri-Sun. Contact: UCSD.

March 13-15—**15th Annual Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Mon-Wed. 18 hrs. $350. Contact: UCSF.

April 16-21—**15th Annual Residents' Radiology Review Course**. UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. 8 hrs. $135. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 184)

SOUTHERN MEDICAL ASSOCIATION

Spring 1995 CME Calendar

PRIMARY CARE PROGRAMS

The following programs contain appropriate information for primary care physicians practicing family medicine, internal medicine, obstetrics & gynecology, pediatrics, or geriatric medicine.

Caring for People With Chronic Health Conditions
March 24-26, 1995 • Hilton Head Island, SC

New Drugs Update: A Clinician's Perspective
March 31-April 2, 1995 • Biloxi, MS

Rehab & Primary Care: Helping People Help Themselves
April 21-23, 1995 • Birmingham, AL

National Interactive Video Conference - The Brain At Risk: Preventing, Diagnosing & Managing Stroke
May 2, 1995

Musculoskeletal Impairment & Disability Evaluation
May 12-14, 1995 • New Orleans, LA

Geriatric Medicine: An Update on Diagnosis & Management
June 8-10, 1995 • San Antonio, TX

SPECIALTY PROGRAMS

The following programs contain in-depth information in a particular specialty, but may also be appropriate for primary care or allied health care professionals.

SEC Sports Medicine Symposium
Target Audience: Orthopaedists, Sports Medicine, Primary Care, Sports Trainers, Physical Therapists
March 9-12, 1995 • Atlanta, GA

5th Annual Mammography Update
Target Audience: Radiologists
March 12-14, 1995 • Amelia Island, FL

The Shoulder Symposium
Target Audience: Orthopaedic Surgeons
April 7-8, 1995 • Pine Mountain, GA

Current Concepts in Orthopaedics
Target Audience: Orthopaedic Surgeons
May 19-21, 1995 • Baltimore, MD

19th Annual Lung Symposium
Target Audience: Pulmonology, Critical Care
June 11-15, 1995 • Sea Island, GA

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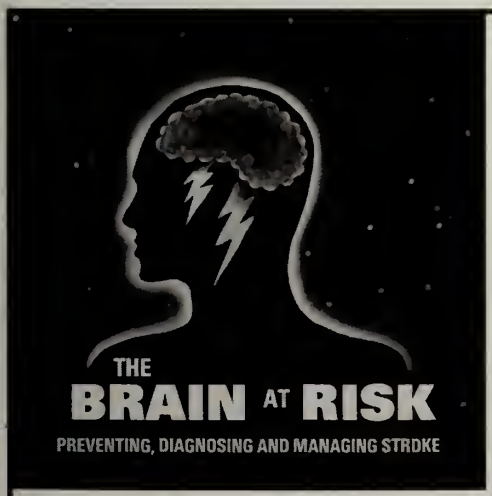

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(Continued from Page 182)

April 21-23—**Mammography Update and Review.** UCSD at Hotel Del Coronado, San Diego. Fri-Sun. 16 hrs. $350. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 16-20—**Advanced Imaging of the Spine**. UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 24 hrs. $550. Contact: UCSD.

SURGERY

March 16-18—**45th Annual Surgical Forum**. Society of Graduate Surgeons of the Los Angeles County and USC at Sheraton Grande Hotel, Los Angeles. Thurs-Sat. 22 hrs. $475 Contact: Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

March 24-25—**7th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Fri-Sat. Contact: UCSF.

April 20-22—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, Nob Hill, San Francisco. Thurs-Sat. Contact: UCSF.

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

May 14-17—**36th Annual Meeting: Society for Surgery of the Alimentary Tract**. UCSD at San Diego Convention Center. Sun-Wed. 23 hrs. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

March 9-10—**Focus on Fungal Infections 5**. International Medical Experience Exchange at Sheraton Palace, San Francisco. Thurs-Fri. 14 hrs. Contact: Anita Reeves, IMEDEX USA, 1060 Cambridge Square. Ste D, Alpharetta, GA 30201. (404) 751-7332.

April 28—**The Cutting Edge 1995: How to Treat Difficult Patient.** UCSD at Pan Pacific Hotel, San Diego. Fri. 13 hrs. $325. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation. 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 20-24—**21st Annual OB/GYN Conference.** University of Colorado Health Sciences Center at Vail. Mon-Fri. Contact: U of Colo.

February 20-24—**19th Midwinter Symposium on Practice Surgical Challenges in Otolaryngology.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Jane Whitener, (312) 996-5751.

February 26-March 3—**Ninth Annual Cardiology for the Clinician Conference: Practical Guidelines for Merging Advances in Cardiology and Bedside Medicine.** University of Illinois College of Medicine at Snowmass. Mon-Fri. Contact: Sue Talbert, (312) 996-4631.

March 5-9—**Neurosurgery in the Rockies**. University of Colorado Health Sciences Center at Vail. Sun-Thurs. Contact: U of Colo.

March 5-10—15th **Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Medical Center, (402) 559-4152 or (800) 642-1095; FAX (402) 559-5915.

March 12-15—**5th International Conference on Pulmonary Rehabilitation and Home Ventilation**. National Jewish Center for Immunology and Respiratory Medicine and American Association for Respiratory Care at Hyatt Regency, Denver. Sun-Wed. Contact: Adele Gelfand. (303) 398-1359 or 270-2171.

March 12-15—**Colorado Conference on Patient-Centered Family Practice**. University of Colorado Health Sciences Center, Denver. Sun-Wed. Contact: U. of Colo.

March 30-April 2—**New Developments in Cancer Biotherapy: The Second Decade**. Presbyterian/St Luke's Medical Center at Beaver Run Resort, Breckenridge. Thurs-Sun. Contact: Mary Fletcher, Presbyterian/St Luke's Medical Center, 1719 E 19th Ave, Denver 80218. (303) 839-6000.

March 31-April 2—**Geriatric and Surgical Urogynecology**. Presbyterian/St Luke's Medical Center at Beaver Run Resort, Breckenridge. Fri-Sun. Contact: Mary Fletcher, Presbyterian/St Luke's Medical Center, 1719 E 19th Ave, Denver 80218. (303) 839-6000.

April 7—**The Female Athlete: Enhancing Health and Fitness**. University of Colorado Health Sciences Center, Denver. Fri. Contact: U of Colo.

July 28-August 1--**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 17-19—**Ada County Medical Society—36th Annual Medical Winter Clinics—From Trauma to Rahab**. Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, members; $175, nonmembers. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930 or Marie Chester, (208) 386-2135..

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

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March 1-4—**New Mexico Metabolism Symposium 1995**. Lovelace Clinic Foundation at Quail Ridge Inn, Taos. Contact: Lettie Dupuy, (505) 262-7746; FAX (505) 262-7598.

March 11-12—**Pediatric Surgery and ENT**. American Academy of Pediatrics and University of New Mexico School of Medicine at Nursing and Pharmacy Building, UNM SOM. Contact: Steven M. Yabek, MD, 715 Grand Ave NE, Ste 207, Albuquerque 87102. (505) 848-3700.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting**. Hilton Hotel of Santa Fe. Sat. Contact: Robin Clifton, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 20-24—**Workshops in Advanced MR Imaging, Head and Neck Imaging, and Neuroradiology.** University of Utah School of Medicine. Mon-Fri. Contact: UUSM.

February 23-March 2—**40th Annual Postgraduate Course in Anesthesiology—Pediatric and Obstetrical Anesthesia: 1995 Update.** University of Utah School of Medicine at Snowbird Cliff Lodge. One week. Contact: UUSM.

February 26-March 1—**36th Annual OB/GYN Update.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 1-4—**OB/GYN Update in Endocrinology and Infertility.** University of Utah School of Medicine at the Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 5-10—**Emergencies in Medicine.** Detroit Receiving Hospital at The Yarrow Resort, Park City. Sun-Fri. Contact: Robert F. Wilson, MD, Dept of Surgery, Detroit Receiving Hospital, 4201 St Antoine, Detroit, MI 48201. (313) 745-3485.

March 6-10—**Advances in Internal Medicine.** University of Utah School of Medicine at Cottonwood Center, Snowbird. Mon-Fri. Contact: UUSM.

March 10—**Ophthalmology—Resident/Alumni Day**. University of Utah School of Medicine. Fri. Contact: UUSM.

March 10-11—**Western Intermountain Neurological Organization**. University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

June 7-10—1995 **Summer Pediatric Neurosurgery Symposium.** University of Utah School of Medicine at Stein Eriksen Lodge in Deer Valley, Park City. Wed-Sat. Contact: UUSM.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 185)

February 24-25—**Renal Update 1995**. Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

February 24-25—**Transplantation Issues, Needs and Opportunities in the African-American Community**. Seattle. Fri-Sat. Contact: Providence, (206) 320-2552.

March 2—**Diagnosis and Treatment of Insomnia in Clinical Practice**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 3-4—**Attention Deficit Hyperactivity Disorder**. Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

March 4-5—**PALS**. Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

March 5-10—**17th Annual Winter Psychiatry Conference: Coping With Current Issues in Clinical Practice**. Park City, Utah. Sun-Fri. Contact: Menninger Continuing Education, (800) 288-7377.

March 6-8—**The Best Approach: Effective, Efficient Strategies in Clinical Practice and Prevention.** Seattle. Mon-Wed. Contact: Group Health, (206) 326-3441.

March 9—**Family Practice Symposium.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 16—**Radiation Safety, Challenge, Change, and Compliance.** Seattle. Thurs. Contact: Providence, (206) 320-2552.

March 17-18—**Treatment of Motor Speech Disorders in Children**. Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

March 23—**Controversial Medical Diagnoses**. Everett. Thurs. Contact: PNMEII, (206) 261-2160.

April 19—**Geriatrics Symposium**. Seattle. Wed. Contact: Providence Hospital, (206) 320-2552.

May 5-6—**Mental Health Update.** U/W. Fri-Sat. Contact: U/W.

May 20-21—**PALS**. Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

June 1-3—**Primary Care Update of OB-GYNs.** Seattle. Thurs-Sat. Contact: U/W.

June 2-3—**6th Update on Travel and International Medicine**. Seattle. Fri-Sat. Contact: U/W.

June 7-10—**Bariatric Medicine**. Seattle. Wed-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 8-10—**Wyoming Medical Society—Annual Meeting**. Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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UNIVERSITY PHYSICIAN. Student Health Service, University of Wyoming, Laramie, is seeking a physician for full-time employment. Applicants must have an MD or DO degree and be BC/BE in a primary care specialty. Must have a license, or qualify for licensure, to practice medicine in the State of Wyoming. Prefer the candidate to have at least two years of primary care experience in college health. Essential duties: examine patients, diagnose illness, and prescribe treatment. Order or conduct tests and x-rays. Analyze reports and finding of tests or examination. Administer or prescribe treatment and drugs, assist with training and instructing professional staff in appropriate specialty and coordinate delivery of health care services. The physician will join three full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy departments. Salary commensurate with qualifications and experience. Closing date is March 8, 1995. Inquiries can be made to: A. Roth, MD, Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, WY 82071. Send applications, CV and three letters of reference to Human Resource Department, PO Box 3422, Laramie, WY 82071. UW is an EO/AA Employer.

NORTHERN CALIFORNIA, SAN FRANCISCO BAY AREA. Well established, busy Family Practice group seeking third member. No OB. Six-member call group. Guarantee, incentive and benefit package. Call Ellen at (707) 643-6483.

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NORTHERN CALIFORNIA, MEDICAL DIRECTOR. Primary Care Group seeks a Director to provide leadership for a growing family practice, primary and urgent care group. Dynamic ambulatory care center with increasing patient volume needs experienced Director to lead physicians, implement policies and procedures, and manage QA. Responsibilities also include maintaining a practice. Redding is beautifully located between Sacramento and the Oregon border. Family oriented, excellent schools, safe and friendly community, affordable housing, and recreational activities. This is a quality of life opportunity. Incentive based compensation, Director stipend, liability insurance, flexible scheduling and no nights. Please call Ellen Montague, Physician Search Consultant (by phone, FAX, or mail a CV) Fischer-Mangold, PO Box 788, Pleasanton, CA 94566. Phone (510) 484-1200 or (800) 227-2092 outside California. FAX (510) 484-4107.

PACIFIC NORTHWEST. Placement specialists serving northern California, Oregon, Washington. City or rural, group or solo. Internal Medicine, Family Practice, OB/GYN, Pediatrics, and all other specialties. Barbara Stoefen, President, The O'Kane Group, 25 NW Minnesota Ave, Ste 7, Bend, OR 97701; (800) 451-0700, FAX (503) 389-5134.

ORTHOPAEDIST–BC/BE, California-licensed, needed for San Francisco-based multispecialty medical practice. Primarily forensic medical practice (evaluation and expert witness evaluations in workers' compensation, personal injury, etc). Excellent opportunity for experienced clinician looking to emphasize evaluation and consultation practice as opposed to heavy treatment-based practice. Full-time and part-time employment available, exceptionally high income potential, full benefits, and 401K. Submit CV and letter stating professional goals and availability to Administrator, 2040 Polk St, Box 337, San Francisco, CA 94109.

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WESTERN WASHINGTON: OB/GYN PHYSICIAN, BC OR BE. Join established physicians, small community near Seattle, very low crime, no state income tax. Excellent schools and very reasonable real estate prices. Less than one hour to coean. Several four-year colleges in area. Call Eva Page, Page & Associates, Physician Recruiting, (800) 833-3449; FAX CV to (206) 746-1397.

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REGIONAL MEDICAL DIRECTOR. Pacific Medical Center and Clinics is a multispecialty group practice with a network of progressive, nonprofit ambulatory care clinics currently with six locations in the Seattle/King County area. We are dedicated to a personalized style of managed care. We have a unique opportunity for a BC/BE Family Practice or Internal Medicine Physician with a minimum five years, demonstrated managed care medical group leadership and management experience. This position will be operationally and strategically responsible for the development of several new primary care clinic sites within South King County. Please send cover letter and CV to: Pacific Medical Center and Clinics, Attn: Human Resources, 1200 12th Ave S, Seattle, WA 98144; FAX (206) 326-4031.

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WESTERN WASHINGTON: FAMILY PRACTICE, OB OPTIONAL, BC OR BE PHYSICIAN to join established doctors. Located near Seattle, small community, very low crime area, no state income tax. Excellent schools and very reasonable real estate prices. Several four-year colleges in area. Less than one hour to ocean. Contact Eva Page, Page & Associates, Physician Recruiting, (800) 833-3449 or send CV to 1420 NW Gilman Blvd, Ste 2133, Issaquah, WA 98027; or call (800) 833-3449; FAX (206) 746-1397.

NAPA VALLEY - CA. Opportunity available immediately for BC/BE Internist. Guaranteed salary. Blend advantages of private practice with efficiency of well-established, small IM group practice. Enjoy small community living only 45 minutes from San Francisco. Send CV Attn: Kris Jones, 3230 Beard Rd, Napa, CA

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Washington/Alaska/Montana/Idaho (WAMI) Clinical Medical Education Coordinator – Boise, Idaho

The University of Washington School of Medicine is looking for a person to initiate, develop and coordinate clinical education experiences in Idaho.

The University of Washington School of Medicine is committed to excellence in biomedical education, research and healthcare. We place special recognition on the importance of primary care and recognize a special responsibility to the people of the states of Washington, Alaska, Montana and Idaho, who have joined with us in a unique regional partnership called the WAMI Medical Education Program. Components of the medical education program in Idaho have grown significantly since the program's inception 22 years ago. Approximately 150 medical students and residents are currently trained each year in six clinical clerkship sites, three residency sites, and approximately 20 Summer preceptor sites throughout the state of Idaho.

Requirements: This is a full-time position. The successful candidate will be a board certified primary care physician with a practice background, administrative experience, and excellent interpersonal skills. Clinical and teaching opportunities will be provided.

Appointment and Reporting Relationships: Academic appointment will be to the clinical faculty of the University of Washington School of Medicine, with adjunct appointment at the University of Idaho. The coordinator will be located in Boise, Idaho and will report to the associate dean for regional affairs and rural health at the University of Washington School of Medicine in Seattle. Regular relationships will be maintained with the WAMI coordinator at the University of Idaho in Moscow, the director of the Idaho Rural Health Education Center in Boise, the University of Washington School of Medicine clinical department coordinators in Seattle, and the clinical clerkship coordinators, preceptors and residency directors throughout Idaho.

Responsibilities: will include, but are not limited to: Coordination of medical student placement at clinical sites in Idaho, including coordination of housing and other student-related details with the Academic Affairs Office at the School of Medicine; site development and evaluation, including initiation, development and coordination of a new six-month rural training program (WRITE); collaboration with Idaho residencies for placement of residents in rural community-based rotations; collaboration with the Idaho Rural Health Education Center in developing interdisciplinary training opportunities; coordination with other institutions of higher education for interdisciplinary student placement; creation of a University of Washington School of Medicine/University of Idaho presence in Boise by meeting with respresentatives of state government, medical groups and the private sector.

Interested candidates should submit a resume and cover letter describing their qualifications for the position, along with the names, addresses and telephone numbers of three references. **Application deadline is March 15, 1995.** Address correspondence to: Thomas E. Norris, M.D., Assistant Dean for Regional Affairs and Rural Health, Office of the Dean, SC-64, University of Washington School of Medicine, Seattle, Washington 98195.

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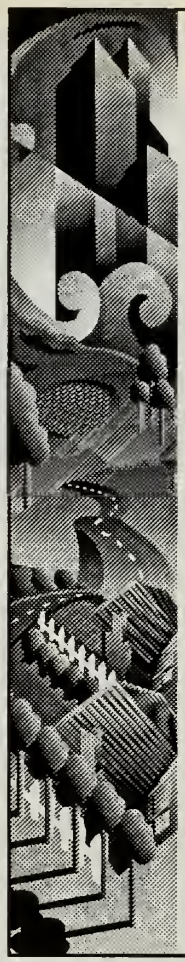

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Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

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Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 28-30, 1995. Spokane Sheraton Hotel, Spokane, Washington.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 8-10, 1995, Jackson Lake Lodge, Moran.

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USC Hand Surgeons

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Stephen Schnall, M.D.
Randy Sherman, M.D.
Milan Stevanovic, M.D.
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The Hand Program at USC University Hospital takes an advanced, comprehensive approach to the diagnosis, treatment and rehabilitation of patients with hand and upper extremity disorders. The program provides a full spectrum of services in one centralized location. This convenience, combined with the academic and research strengths of the USC School of Medicine, represents a unique resource for Southern California.

The Hand Program features the interdisciplinary services of professionals with specialized training in hand and upper extremity injury management. These professionals include plastic surgeons, orthopaedic surgeons, neurosurgeons, certified hand therapists, case managers and psychologists who care for patients with both acute and chronic disorders.

Chronic conditions include carpal tunnel syndrome, peripheral nerve injuries, tendinitis, bursitis, epicondylitis and de Quervain's disease, as well as chronic trauma problems caused by inflammation of the joint linings or tendon sheaths. Other disorders treated are Dupuytren's contracture, pain syndromes, reflex sympathetic dystrophy, congenital anomalies, sports injuries, and bone and tendon injuries. Acute injuries include limb or digit loss and burns.

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Hand Rehabilitation Center

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• **Hand and Upper Extremity Rehabilitation** — The average length of treatment in the program is seven days. This can vary from a single visit for splint construction or ergonomic analysis and education to several months for complex and disabling injuries. Services include comprehensive upper extremity evaluations and therapy, static and dynamic splinting, desensitization, whirlpool/wound care, active functional activities and computer-assisted exercise equipment.

• **Return-To-Work Program** — This program is closely affiliated with the Hand and Upper Extremity Rehabilitation Program, but functions as a separate entity. It is designed for patients with residual impairment or whose recovery may have been prolonged. A team consisting of registered occupational therapists and certified vocational evaluators, assisted by certified occupational therapy assistants and technicians, provides both work hardening and dominance retraining programs. Various assessment services are available to help determine whether an injured person is ready for work, and what equipment or modifications may be required to permit employment.

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In Memoriam

California Medical Association

Abramson, Mason H., Redwood City. Died Dec 11, 1994, aged 78. Graduate of Stanford University School of Medicine, Stanford, California, 1942. Licensed in California in 1942. Dr Abramson was a member of the San Mateo County Medical Association.

Bowers, Richard E., San Diego. Died Oct 30, 1994, aged 74. Graduate of Loma Linda University School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Dr Bowers was a member of the San Diego County Medical Society.

Cappeller, William S., San Francisco. Died Aug 14, 1994, aged 84. Graduate of Harvard Medical School, Boston, Massachusetts, 1938. Licensed in California in 1941. Dr Cappeller was a member of the San Francisco Medical Society.

Franco, Jorge, San Jose. Died Dec 20, 1994, aged 65. Graduate of San Marcos Medical School, Lima. Licensed in California in 1958. Dr Franco was a member of the Santa Clara County Medical Association.

Hanshaw, Truman, R., Fresno. Died Jan 3, 1995, aged 79. Graduate of Loma Linda University School of Medicine, Los Angeles, 1944. Licensed in California in 1945. Dr Hanshaw was a member of the Fresno-Madera Medical Society.

Hirsch, e. leah, Oakland. Died Nov 24, 1994, aged 74. Graduate of Women's Medical College of Pennsylvania, Philadelphia, 1946. Licensed in California in 1948. Dr Hirsch was a member of the Alameda-Contra Costa Medical Association.

Hooper, Charles J., Fresno. Died Jan 11, 1995, aged 46. Graduate of University of California, Davis, School of Medicine, 1976. Licensed in California in 1977. Dr Hooper was a member of the Fresno-Madera Medical Society.

Kay, Harold, Piedmont. Died Dec 23, 1994, aged 85. Graduate of University of California, San Francisco, School of Medicine, 1936. Licensed in California in 1936. Dr Kay was a member of the Alameda-Contra Costa Medical Association.

Koos, Frank A., Arroyo Grande. Died Dec 27, 1994, aged 60. Graduate of Loma Linda University School of Medicine, Los Angeles, 1960. Licensed in California in 1961. Dr Koos was a member of the San Luis Obispo County Medical Society.

Lord, Cecil J., Riverside. Died Jan 5, 1995, aged 87. Graduate of Queen's University and Royal Victoria Hospital, Ireland, 1929. Licensed in California in 1941. Dr Lord was a member of the Riverside County Medical Association.

Mathews, Roy E., Sacramento. Died Dec 23, 1994, aged 64. Graduate of Loma Linda University School of Medicine, Los Angeles, 1956. Licensed in California in 1959. Dr Mathews was a member of the Sacramento-El Dorado Medical Society.

Matzinger, Philip., Oakland. Died Dec 17, 1994, aged 86. Graduate of Northwestern University Medical School, Chicago, Illinois, 1938. Licensed in California in 1938. Dr Matzinger was a member of the Alameda-Contra Costa Medical Association.

Nahman, Morton S., San Francisco, Died Dec 19, 1994, aged 79. Graduate of University of California, San Francisco, School of Medicine, 1941. Licensed in California in 1941. Dr Nahman was a member of the San Francisco Medical Society.

Nelson, Marti W., Vacaville. Died Nov 9, 1994, aged 40. Graduate of Louisiana State University School of Medicine, Shreveport, 1982. Licensed in California in 1986. Dr Nelson was a member of the Solano County Medical Society.

Pennisi, Vincent, San Francisco. Died Dec 26, 1994, aged 71. Graduate of Georgetown University School of Medicine, Washington, DC, 1950. Licensed in California in 1955. Dr Pennisi was a member of the San Francisco Medical Society.

Rothenberg, Sam, Fresno. Died Dec 20, 1994, aged 71. Graduate of University of Colorado School of Medicine, Denver, 1947. Licensed in California in 1948. Dr Rothenberg was a member of the Fresno-Madera Medical Society.

Rummell, Philip, Sunriver, Oregon. Died Jan 4, 1995, aged 77. Graduate of University of Oregon Medical School, Portland, 1943. Licensed in California in 1948. Dr Rummell was a member of the Humboldt-Del Norte Medical Society.

Sheppard, Haynes W., Poway. Died Aug 1994, aged 86. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1944. Licensed in California in 1955. Dr Sheppard was a member of the San Diego County Medical Society.

Shev, Edward E., San Francisco. Died Dec 2, 1994, aged 75. Graduate of University of Nebraska College of Medicine, Omaha, 1945. Licensed in California in 1947. Dr Shev was a member of the San Francisco Medical Society.

Tanaka, Paul A., Santa Barbara. Died Jan 9, 1995, aged 84. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1935. Licensed in California in 1936. Dr Tanaka was a member of the Santa Barbara County Medical Society.

Vanpelt, James F., Jr, Corona. Died Dec 10, 1994, aged 76. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1950. Licensed in California in 1963. Dr Vanpelt was a member of the Riverside County Medical Association.

Walther, Neal J., Visalia. Died Oct 25, 1994, aged 53. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1966. Licensed in California in 1972. Dr Walther was a member of the Tulare County Medical Society.

Zeitsoff, Leslie, Stockton. Died Nov 18, 1994, aged 80. Graduate of University of California, Urvine-California College of Medicine, 1962. Licensed in Calfornia in 1975. Dr Zeitsoff was a member of the San Joaquin County Medical Society.

New Mexico Medical Society

McDowell, James F., Las Cruces. Died Sep 19, 1994, aged 71. Graduate of University of Louisville School of Medicine, Louisville, Kentucky. Licensed in New Mexico in 1957. Dr McDowell was a member of the Dona Ana County Medical Society.

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New Drugs Update: A Clinician's Perspective
March 31-April 2, 1995 • Biloxi, MS

Rehab & Primary Care: Helping People Help Themselves
April 21-23, 1995 • Birmingham, AL

Video Teleconference - The Brain At Risk: Preventing, Diagnosing & Managing Stroke
May 2, 1995

Musculoskeletal Impairment & Disability Evaluation
May 12-14, 1995 • New Orleans, LA

Geriatric Medicine: An Update on Diagnosis & Management
June 8-10, 1995 • San Antonio, TX

SPECIALTY PROGRAMS

The following programs contain in-depth information in a particular specialty, but may also be appropriate for primary care or allied health care professionals.

The Shoulder Symposium
Target Audience: Orthopaedic Surgeons
April 7-8, 1995 • Pine Mountain, GA

Current Concepts in Orthopaedics
Target Audience: Orthopaedic Surgeons
May 19-21, 1995 • Baltimore, MD

19th Annual Lung Symposium
Target Audience: Pulmonology, Critical Care
June 11-15, 1995 • Sea Island, GA

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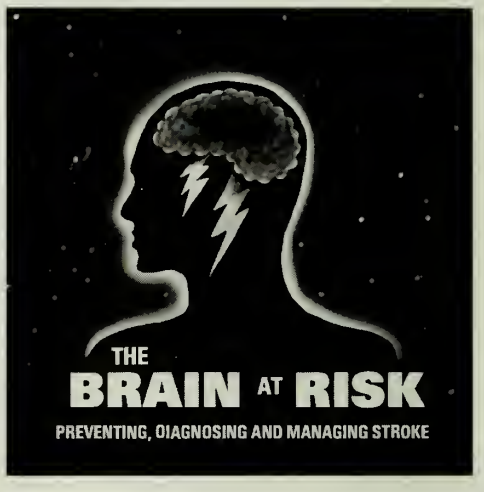

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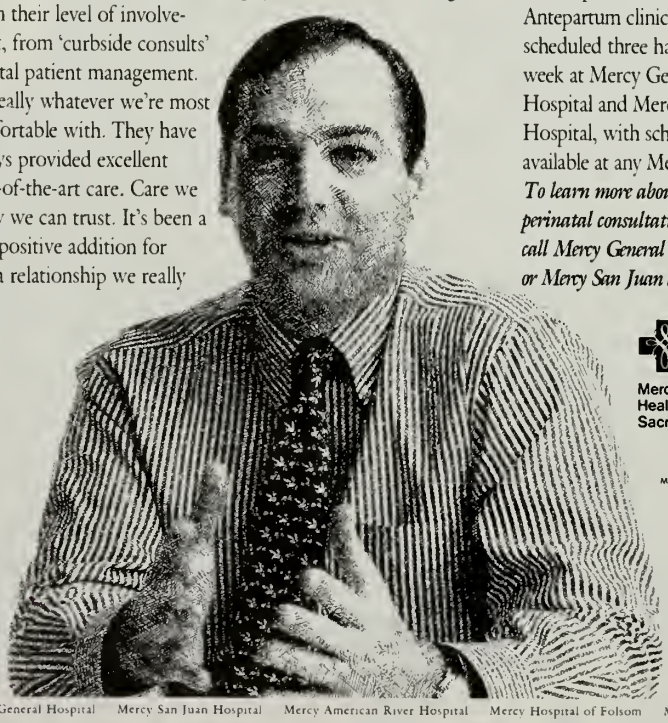

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In the battle against allergic rhinitis

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Symptomatic relief superior to QD non-sedating antihistamines

See charts on reverse side

QD staying power

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Onset of action as early as 12 hours

Maximum benefit is generally seen within 3 to 4 days

Excellent safety profile

No measurable effect on HPA function at recommended doses

The most commonly reported side effects are headache and nasal irritation

ONCE DAILY

Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Please see brief summary of prescribing information on following page.

1 ONCE DAILY Nasacort® Nasal Inhaler

(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using
BRIEF SUMMARY

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler.

Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).

Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations.

Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days).

The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects.

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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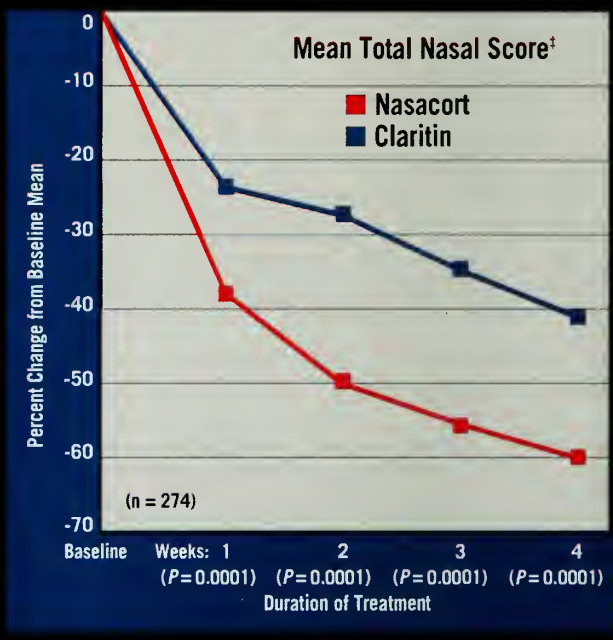
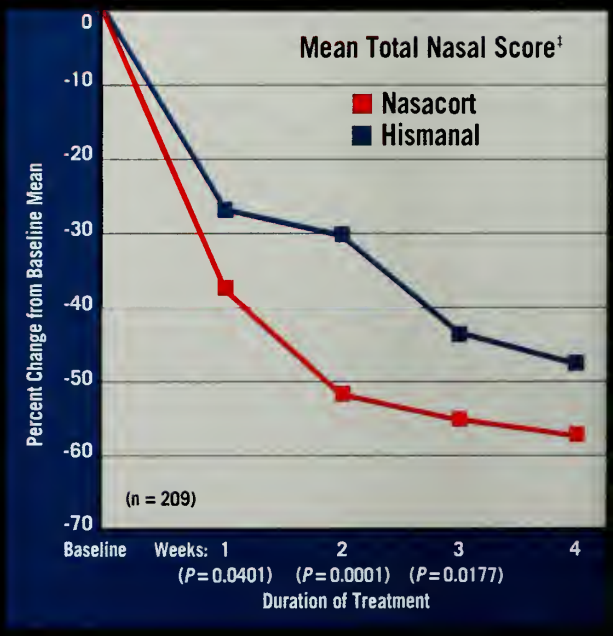
Superior symptomatic relief vs. QD non-sedating antihistamines[1]

NASACORT VS. CLARITIN[1]*



‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[2]§



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*

† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*

§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

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1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis *1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom D, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function.* J Allergy Clin Immunol *1992;89(6):1151-1156.*

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 16-18—**22nd Annual Symposium—Recent Advances in Neurology and Neurosurgery**. University of Arizona and Barrow Neurological Institute at Marriott's Camelback Inn, Scottsdale. Thurs-Sat. Contact: Beverly Pennington, (602) 406-3067.

March 17-19—19th **Annual James H. McDonald Urological Seminar.** Maricopa Medical Center and Phoenix Urologic Society at Scottsdale Plaza Resort. Fri-Sun. Contact: Beverlee Anderson, (602) 267-5366.

March 18—**Miles Communication Seminar.** Miles Institute of Healthcare Communication and the Mutual Insurance Company of Arizona at the Ritz Carlton Hotel, Phoenix. Sat. Contact: Shawn Fleishon, (602) 956-5276 or (800) 352-0402.

March 25-30—**Skeletal Radiology.** Allegheny General Hospital and Medical College of Pennsylvania at the Arizona Biltmore, Phoenix. Sat-Thurs. Contact: (412) 359-4952.

March 30-April 1—**4th Annual Urogynecology and Disorders of the Pelvic Floor**. Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Tues-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30-April 2—**Mammography in March: Breast Diseases and Imaging.** Maricopa Medical Center at Marriott Camelback Inn, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

April 2-7—**Management Development for Department Chairs Programs A and B.** American College of Physicians Executives at the Wyndham Paradise Valley Resort, Scottsdale. Sat-Fri. Contact: (800) 562-8088.

April 4-7—**Current Issues in Primary Care Medicine**. Pacific Northwest Medical Education Institute, Inc, at the Pointe Hilton at Squaw Peak, Phoenix. Tues-Fri. Contact: (206) 261-2160.

April 4-8—**1995 Annual Meeting—Arizona Osteopathic Medical Association**. Wyndham Paradise Valley Resort, Scottsdale. Tues-Sat. Contact: (602) 840-0460.

April 5-8—**Primary Care Update.** University of Arizona College of Medicine at the Tucson East Hilton. Wed-Sat. Contact: Lynne Mascarella, U of A.

April 6-8—**Lower Extremity Arthroplasty**. Mayo Foundation, Scottsdale. Thurs-Sat. Contact: (800) 323-2688.

April 6-9—**2nd Mayo Telemedicine Symposium and 2nd International Symposium on the Medical Aspects of Telemedicine**. Mayo Foundation. Sat-Tues. Contact: (800) 323-2688.

April 7-11—**1995 Annual Meeting—South Central Association of Blood Banks**. The Pointe at South Mountain, Phoenix. Fri-Tues. Contact: (512) 459-6600.

April 9-12—**Management Strategies in Complex Congenital Heart Disease**. Mayo Foundation, Scottsdale. Sun-Wed. Contact:: (800) 323-2688.

April 10-14—**Physician in Management Seminar III**. American College of Physician Executives at the Wyndham Paradise Valley Resort, Scottsdale. Mon-Fri. Contact: (800) 562-8088.

April 19-23—**Women's Health**. American Academy of Family Physicians at The Buttes, Tempe. Wed-Sun. Contact: (800) 926-6890, ext 5245.

April 20-22—**5th Annual Advances and Controversies in Clinical Nutrition.** Mayo Clinic/Mayo Foundation, Phoenix. Thurs-Sat. Contact: (800) 462-9633.

April 22—**Fifth Annual Arizona HPV and Cervical Cancer Conference: New Approaches.** Scottsdale Memorial Hospital. Sat. Contact: Diane, (602) 994-8330.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

June 23-25—**18th Annual Pediatrics in the Red Rocks**. American Academy of Pediatrics, Arizona Chapter, and Maricopa Medical Center at Los Abrigados Resort, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 18-21—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $350. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691

May 19-21—**42nd Annual Meeting of the Association of University Anesthesiologists.** UCSD at Hyatt Regency, San Diego. Fri-Sun. 17 hrs. $400. Contact: UCSD.

May 21-26—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 37.5 hrs. $500. Contact: UCSD.

CARDIOLOGY

April 6-7—**Advanced Techniques in Angioplasty**. Cedars-Sinai Medical Center at Hotel Sofitel Ma Maison, Los Angeles. Thurs-Fri. 15.5 hrs. Contact: Bari Laner, Cedars-Sinai, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937

(Continued on Page 210)

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How to Interpret Stress Echo *Linda Crouse, M.D., Mid-America Cardiology Associates., Kansas City, Mo.*
Arbutamine - A New Stress Agent
Leonard Ginzton, M.D., Harbor UCLA Medical Center, Torrance, Ca.
Stress Echo: Diagnostic and Prognostic Applications
Janine Krivokapich, M.D., UCLA Medical Center, Los Angeles, Ca.
Stress Echo: Who is Being Stressed?
Charles Pollick, M.D., Good Samaritan Hospital
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CONTINUING MEDICAL EDUCATION

(Continued from Page 208)

April 28-30—**Arrhythmias: Interpretation, Diagnosis and Management**. Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

May 11-13—**5th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12—**Stress Echo: Meet the Experts**. Hospital of the Good Samaritan. Fri. Contact: Charles Pollick, (213) 977-2335

DERMATOLOGY

June 9-11—**3rd Annual Skin Rejuvenation Seminar**. Medical Education Resources at Cosmetic Surgery Group of Newport Beach. Fri-Sun. 19 hrs. $2200. Contact: Martin Borsanyi, c/o The Professional Image, (714) 760-1522

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

April 5-8—**11th Annual Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 20 hrs. $495. Contact: UCSF.

May 8-12—**Emergency Medicine Symposium I**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 16-17—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at San Francisco. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

June 19-23—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-21—**High Risk Emergency Medicine and Acute Care**. American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

July 26-30—**Wilderness Medicine 1995**. American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

August 23-24—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians and Emergency Physicians' Medical Group at Pan Pacific Hotel, San Diego. Wed-Thurs. 15 hrs. $295-$495. Contact: Alpen Meeting Service, (800) 451-7475.

EPIDEMIOLOGY/INFECTIOUS DISEASE

April 2-4—**5th Annual Meeting of the Society for Healthcare: Epidemiology of America.** UCSD at Town & Country, San Diego. Sun-Tues. 17 hrs. $435. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

March 29-31—**Annual Review in Family Medicine**. UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $325. Contact: UCSF.

March 30-April 1—**45th Yosemite Postgraduate Institute**. Fresno-Madera Medical Society at Yosemite National Park. Thurs-Sat. 12 hrs. $200-$250. Contact: Carol Rau, 3425 North First St, PO Box 31, Fresno 93707. (209) 224-4224.

April 10-13—**Primary Care in Paradise: Maui 1995.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 16-21—**8th Annual Primary Care Medicine: Update 1995.** UCSF at Inter-Continental Resort, Maui, Hawaii. Sun-Fri. 20.5 hrs. $545. Contact: UCSF.

April 21—**Preventive Health Screening in the Elderly**. UCD at Cancer Center Auditorium, Sacramento. 7 hrs. Contact: UCD.

April 27-30—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

May 10-13—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

May 12-13—**Primary Care for the 90s.** University of Nevada School of Medicine at Hyatt Regency at Lake Tahoe, Incline Village, Nevada. Fri-Sat. 11 hrs. $250. Contact: Continuing Education, Manville Bldg/342, UNSM, NV 89557. (702) 784-4605.

May 20—**Gynecology for Primary Care**. UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. Contact: UCD.

June 11-16—**19th Annual Fingers to the Toes: Orthopaedics for Primary Care**. UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. Contact: UCD.

July 7-9—**39th Annual Postgraduate Symposium of the San Diego Academy of Family Physicians.** Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-300. Contact: Terry Camarata, PO Box 5996, Chula Vista 91912. (619) 422-1186.

July 10-13—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425. Contact: UCSF.

August 4-6—**Cardiology for the Family Physician and Internist**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 210)

August 7-9—**Dermatology for the Non-Dermatologists**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Primary Care Medicine: A Practical Approach**. Scripps Clinic and Research Foundation at Le Meridien San Diego at Coronado. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 21-23—**Sports Medicine and Industrial Medicine for Primary Care Physicians**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

HEMATOLOGY

March 30-April 1—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Thurs-Sat. 18 hrs. $500. Contact: UCSD.

INFECTIOUS DISEASE

April 26-28—**16th Annual Advances in Infectious Dieseases**. UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 16 hrs. $410. Contact: UCSF.

June 7—**9th Annual AIDS Conference: Challenge for Today—Hope for Tomorrow.** Alta Bates Medical Center at Mills College, Oakland. Wed. 7 hrs. Contact: Caroline Carey, (510) 204-3884.

INTERNAL MEDICINE

March 25-April 1—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Hapuna Prince Hotel, Kamuela, Hawaii. Sat-Sat. 29 hrs. $595. Contact: USC.

April 8—**Clinical Nutrition.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. $125. Contact: UCD.

April 22-23—**Minimal Intervention in Vascular Disease.** Scripps Memorial Hospital and Scripps Clinic and Research Foundation at Hyatt Regency, San Diego. Sat-Sun. Contact: Laurel Steigerwald, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 22-26—**23rd Annual Advances in Internal Medicine**. UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 33 hrs. $645. Contact: UCSF.

ONCOLOGY

April 10-14—**20th Annual Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

April 1—**Ophthalmology Laser Course**. UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. Contact: UCD.

May 6—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-2—**Annual Ophthalmology Symposium**. UCD at Vizcaya, Sacramento. Thurs-Fri. Contact: UCD.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

(Continued on Page 212)

CSIM's 1995 ANNUAL MEETING

Don't miss the celebration! Join us in the City by the Bay for CSIM's 50th Annual Meeting at the Grand Hyatt on Union Square. Network with other internists, earn up to six (6) Category 1 CME credits, and get the latest in clinical and socioeconomic information relating to internal medicine. Bring your family and friends and experience San Francisco. Courses include:

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(Continued from Page 211)

ORTHOPEDICS

May 18-21—**10th Annual Symposium of the Spine Study Group**. Spine Study Group at Westin Mission Hills, Rancho Mirage. Thurs-Sun. Contact: Pat Curl, Meeting Coordinator, 4805 Mercury St, Ste E, San Diego 92111. (619) 279-9955.

OTOLARYNGOLOGY

March 26-31, May 7-12—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach**. UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

November 2-4—**San Francisco Otology-Neurotology—1995.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 24 hrs. Contact: UCSF.

PATHOLOGY

April 1—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 25-27—**Current Issues in Anatomic Pathology: 1995**. UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF

August 12-19—**16th Annual Comprehensive Fine Needle Biopsy Course**. UCSF at Ritz-Carlton, San Francisco. 1 wk. 27 hrs. $950. Contact: UCSF.

PEDIATRICS

March 31-April 1—**Pediatric Dermatology for the Practitioner.** Children's Hospital and Health Center and UCSD at Hyatt Regency, La Jolla. Fri-Sat. 12.75 hrs. $245. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

May 4-6—**28th Annual Advances and Controversies in Clinical Pediatrics**. UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

July 21-22—**3rd Annual Pediatrics Update**. Stanford University at Lucile Packard Children's Hospital. Fri-Sat. Contact: Elinor Meyer, Continuing Medical Education, 725 Welch Road, Palo Alto 94304. (415) 497-8554.

PSYCHIATRY AND NEUROLOGY

March 30-April 1—**Volcanoes and Tidal Waves: Contemporary Challenges in Psychiatry**. Hawaii Medical Association at Hilton Hawaiian Village, Honolulu. Thurs-Sat. 12 hrs. Contact: Jan Estioko, 1360 S Beretania St, 2nd Fl, Honolulu, HI 96814. (808) 536-7702.

March 31-April 2—**West Coast Psychiatry Board Review: Preparation for Part II**. UCSD at La Jolla Marriott. Fri-Sun. 16 hrs. $525. Contact: UCSD.

April 7-9—**West Coast Neuropsychology Conference: New Advances in the Assessment and Treatment of Cognitive Deficit in School-Age Children**. UCSD at Pan Pacific Hotel, San Diego. 14.5 hrs. $325. Contact: UCSD.

April 20-25—**37th International Congress on Alcohol and Drug Dependence**. UCSD Extension, La Jolla. Thurs-Tues. 27 hrs. $450. Contact: UCSD.

May 6-7, May 20-21—**32nd Annual Basic Workshop in Clinical Hypnosis.** San Francisco Academy of Hypnosis at Alta Bates Medical Center, Berkeley. Sat-Sun. $250. Contact: Jan Brooks, SFAH-ERF, 615 27th St, San Francisco 94131. (415) 282-3399.

May 24-26—**14th Annual Child Abuse and Neglect Conference.** UCD at Red Lion Hotel, Sacramento. Wed-Fri. 15 hrs. Contact: UCD.

July 25-30—**Neuropsychiatric Emergencies and Crisis Update and Review**. Southern California Neuropsychiatric Institute at Mauna Kea, Hapuna Beach Hotel, Hawaii. Tues-Sun. Contact: Ann McCormick, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102

PULMONARY MEDICINE

March 23-29—**National Association of Medical Directors for Respiratory Care**. University of Nebraska Medical Center at Silverado Hotel, Napa Valley. Fri-Wed. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

RADIOLOGY

April 16-21—**15th Annual Residents' Radiology Review Course**. UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. 8 hrs. $135. Contact: Dawne Ryals, P.O. Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 21-23—**Breast Imaging and Intervention.** UCSD at Hotel del Coronado. Fri-Sun. 15 hrs. $375. Contact: UCSD.

April 22—**UCSD Spring Invasive Radiology Course**. UCSD at Hotel del Coronado. Sat. 6.25 hrs. $135. Contact: UCSD.

July 16-20—**Advanced Imaging of the Spine**. UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 24 hrs. $550. Contact: UCSD.

SURGERY

April 20-22—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, Nob Hill, San Francisco. Thurs-Sat. Contact: UCSF.

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

May 14-17—**36th Annual Meeting: Society for Surgery of the Alimentary Tract**. UCSD at San Diego Convention Center. Sun-Wed. 23 hrs. Contact: UCSD.

June 14-17—**12th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency, La Jolla. Wed-Sat. Contact: Rebecca Quiring, 3905 Waring Road, Oceanside 92056. (619) 940-2066.

GENERAL/MULTIDISCIPLINARY

April 28—**The Cutting Edge 1995: How to Treat Difficult Patient.** UCSD at Pan Pacific Hotel, San Diego. Fri. 13 hrs. $325. Contact: UCSD.

June 2-4—**8th Annual Medical Office Laboratory.** San Diego State University at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $475. Contact: Nanacy Geiser, College of Extended Studies, (619) 594-6255.

June 23—**The Future of American Medicine: A Bioethics Symposium**. UCD at Cancer Center Auditorium. Fri. 3 hrs. Contact: UCD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

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COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

March 16—**Third Annual Ethics Conference: Ethical Dilemmas/Individuals and Organizations Navigating Healthcare Change** Presbyterian/St Luke Medical Center, Denver. Thurs. Contact: Presbyterian/St Luke Medical Center, CME Office, (303) 869-2244.

March 30-April 2—**New Developments in Cancer Biotherapy: The Second Decade**. Presbyterian/St Luke's Medical Center at Beaver Run Resort, Breckenridge. Thurs-Sun. Contact: Mary Fletcher, Presbyterian/St Luke's Medical Center, 1719 E 19th Ave, Denver 80218. (303) 839-6000.

March 31-April 2—**Geriatric and Surgical Urogynecology**. Presbyterian/St Luke's Medical Center at Beaver Run Resort, Breckenridge. Fri-Sun. Contact: Mary Fletcher, Presbyterian/St Luke's Medical Center, 1719 E 19th Ave, Denver 80218. (303) 839-6000.

April 7—**The Female Athlete: Enhancing Health and Fitness**. University of Colorado Health Sciences Center, Denver. Fri. Contact: U of Colo.

July 28-August 1--**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.1925, Roswell, GA 30077-1925. (404) 641-9773.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting.** Hilton Hotel of Santa Fe. Sat. Contact: Robin Clifton, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

May 11-13—**New Mexico Medical Society Annual Meeting.** New Mexico Medical Society, Albuquerque. Thurs-Fri. Contact: Robin Clifton, 7770 Jefferson NE, Ste, 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Fri-Sat.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 281)

Physicians' Advantage and CMA announce

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UCSF

CME CALENDAR

1995 Continuing Medical Education Programs Presented by the Department of Medicine, University of California, San Francisco, School of Medicine.

For further information, or a more detailed program brochure, contact the Department of Medicine Postgraduate Programs Office at 415.476.5208 or FAX them at 415.476.3542.

Sponsored by the University of California School of Medicine at San Francisco Office of Continuing Medical Education. CME Credits vary per course.

Topic	Date	Location
Diabetes Update, Advances in Endocrinology & Metabolism	March 17-18	Ritz-Carlton, San Francisco
Emergency Medicine The Next 100 Years Paramedic Centennial Program	March 23-24	Holiday Inn, Financial District San Francisco
Primary Care Cardiology	April 1	ANA Hotel, San Francisco
Advances in Emergency Medicine	April 5-8	Ritz-Carlton, San Francisco
Primary Care Update	April 16-21	Inter-Continental Hotel, Maui, Hawaii
Advances in Infectious Diseases	April 26-28	Fairmont Hotel, San Francisco
Advances in Internal Medicine	May 22-26	Ritz-Carlton, San Francisco
Advances in Internal Medicine	June 19-23	UCSF Campus, San Francisco
Critical Care Cardiology	August 10-12	Ritz-Carlton, San Francisco
Essentials of Primary Care	August 20-25	Squaw Valley, California
Clinical Care of the AIDS Patient	August 24-29	Sun Valley, Idaho
Design and Methods of Clinicial Trials	September 14-15	Sir Francis Drake, San Francisco

Articles

Hypertension

Preoperative Assessment and Perioperative Management

LAWRENCE LASLETT, MD, *Davis, California*

Presented at the University of California, Davis, conference, Medical Evaluation of the Preoperative Patient, in Carmel, California, October 1993.

Hypertension is a frequently encountered abnormality in patients being prepared for surgical procedures. This condition complicates anesthetic and postoperative management, but careful monitoring and treatment allow hypertensive patients to tolerate surgery safely. Particular attention should be directed toward continuing antihypertensive medicine until the time of the surgical procedure or initiating treatment before it, monitoring the blood pressure frequently after the operation, and controlling postoperative hypertension with one of many parenteral agents available. The possibility of the presence of secondary hypertension and cardiovascular complications of hypertension should be considered during the preoperative assessment.

(Laslett L: Hypertension—Preoperative assessment and perioperative management. West J Med 1995; 162:215-219)

Hypertension is a common abnormality, being present in 50 million Americans.[1(p12)] It is thus frequently detected among patients undergoing preoperative evaluation for surgical procedures—in a quarter of instances in one study.[2] Hypertension in these patients raises several concerns, including the propensity to have more difficult hemodynamic control during anesthesia, a perceived risk of increased intraoperative and postoperative cardiovascular events, difficulties with blood pressure management immediately after the procedure, and the fact that hypertension is a risk factor for the presence of other cardiovascular diseases that may be silent. It is prudent, then, for physicians, surgeons, and anesthesiologists to carefully evaluate the finding of increased blood pressure in patients presenting for surgical procedures.

Assessing Blood Pressure

Physicians must first confirm that patients' hypertension actually exists. Patients may be anxious, fearful, in pain, or rushed during an initial evaluation, all of which can induce a "physiologic" increase in blood pressure not representing true hypertension.[3] Generally a physician can determine this by putting the patient at ease with reassurance and a calm environment, relieving pain if it exists, allowing a period of time to pass, then repeating the blood pressure measurement. In addition, the long-term state of the blood pressure may be determined by reviewing the patient's medical records. In these ways, a patient initially thought to be hypertensive may be found to have a normal blood pressure.

The basic principles of blood pressure measurement, such as the use of a proper-sized cuff, must not be forgotten. Although a patient found hypertensive only transiently on admission may not need specific antihypertensive therapy to be prepared for a surgical procedure, this finding alone does indicate a propensity to become hypertensive during anesthesia and surgical therapy and should alert those caring for the patient to be prepared for the possible need to treat excessive rises in blood pressure.[4] Particularly for patients undergoing a serious surgical procedure, blood pressure is often monitored directly through an intra-arterial catheter beginning immediately before anesthesia and continuing into the early postoperative course. This ensures that rapid changes in the blood pressure are detected and obviates the possibility of inaccurate cuff measurements due to body habitus or upper extremity vascular rigidity.

Blood Pressure Response to Surgical Procedures

If a patient is found preoperatively to have a truly elevated blood pressure, possible risk from this can be considered in two phases—the anesthetic and the postoperative periods. It is not unusual for a patient undergoing anesthesia to have a fall in blood pressure during induction, followed by a pressor response and tachycardia with intubation, a stabilization of blood pressure and heart rate during anesthesia, and another rise in these measurements during awakening and extubation. In a patient with hypertension, these changes are

From the Division of Cardiovascular Medicine, Department of Internal Medicine, University of California, Davis, School of Medicine.
Reprint requests to Lawrence Laslett, MD, Division of Cardiovascular Medicine, UCD Professional Bldg, 4301 X St, Sacramento, CA 95817.

exaggerated.[5] This is most prominent in patients with untreated hypertension who are seen for surgical therapy, but to a lesser extent it also occurs in those whose blood pressure, though treated, remains uncontrolled. Although persons with effectively treated hypertension have blood pressure changes more similar to those with normal blood pressures,[5] they, too, may have problematic lability in pressure. These excessive swings in blood pressure and heart rate place a patient with coronary artery disease or left ventricular dysfunction at risk for ischemia or heart failure.[6] Indeed, hypertensive patients have shown an increased incidence of ST-segment depression during surgical procedures while electrocardiographically monitored.[7] In addition, chronic hypertension resets cerebral circulatory autoregulation so that in these patients intraoperative and postoperative blood pressure reductions to otherwise benign levels may induce cerebral ischemia.[8,9]

Surgical Risk for Hypertensive Patients

These risks have led to a concern as to whether hypertensive patients should undergo elective surgical procedures. Fortunately, data available indicate that at least patients presenting with mild or moderate hypertension can safely undergo surgical procedures. In a landmark study of 1,001 patients undergoing noncardiac operations, preoperative evaluation detected 280 with current or past elevated blood pressures.[2,10,11] Although several other criteria predicted a perioperative cardiac event, in multivariate analysis, hypertension did not. Other studies have since confirmed this finding.[12,13]

Presumably the explanation for this favorable result, despite the possible risk from increased hemodynamic instability associated with hypertension, is that modern anesthetic skills and techniques allow an anesthesiologist to blunt the exaggerated hemodynamic swings of hypertensive patients and to detect evidence of ischemia or congestive failure early so that pharmacologic intervention can be used to reverse these processes. Obviously, it is important for the anesthesiologist to be aware of the patient's hypertension preoperatively so that adequate anesthetic planning can be done to ensure safety.

As previously mentioned, patients with hypertension who undergo surgical procedures with their blood pressure controlled have less serious hemodynamic changes intraoperatively than patients with uncontrolled hypertension going into surgery.[5] If the surgical procedure is elective, it should be postponed until medical management of the hypertension is effective and metabolic homeostasis has occurred, probably a few weeks. β-Blockade—in those expected to tolerate such therapy well—may offer a particular advantage in smoothing intraoperative hemodynamics.[14]

If medical, logistic, personal, or reimbursement concerns suggest that an operation proceed as originally scheduled, several studies have shown the efficacy of short-term (within hours before the operation) treatment of hypertension by intravenous β-blockade[15] and by oral β-blockers[16,17] and clonidine hydrochloride[18] in smoothing the blood pressure and heart rate responses during anesthesia. β-Blockade also was shown to notably limit the magnitude of blood pressure rise during intubation and the amount of ischemic changes on electrocardiographic monitoring during a surgical procedure.[16,17,19] This benefit likely also results from using other agents shown to smooth intraoperative hemodynamics,[20] because excessive blood pressure and heart rate changes are the probable stimuli of most episodes of intraoperative ischemia.

Continuing Antihypertensive Therapy Until Surgery

Despite evidence that patients taking antihypertensive agents should continue them until immediately before an operation, this practice is still not uniformly accepted. In the past, various authorities advocated discontinuing antihypertensive medicines for days to weeks before elective operations because of severe hemodynamic instability occurring during anesthesia in some patients taking antihypertensive medicine up until a surgical procedure.[21,22] The patients evaluated, however, were primarily taking reserpine, an agent that rendered them particularly prone to such complications and that now is seldom used. With knowledge of the medicine being taken by the patient, anesthetic techniques can accommodate to this problem.[23] Furthermore, the withdrawal of some antihypertensive agents such as β-blockers or clonidine can cause rebound hypertension or unmask myocardial ischemia that may not have been previously recognized. Thus, it is now clear that patients should be maintained on their blood pressure medicines until the time of a surgical procedure, even with a small sip of water during the preoperative period when they are allowed nothing by mouth.

Postoperative Management

Although patients with hypertension engender the concern already discussed of ischemia during a surgical procedure, it is during the hours and first few days after an operation that most episodes of surgically related myocardial infarction occur.[24,25] Several factors may contribute to this risk, including oxygenation problems, tachycardia, and altered thrombotic potential, but prominent is hypertension. Hypertension directly raises the myocardial oxygen demand. In the presence of coronary artery disease, this demand may not be able to be met. Postoperative hypertension may also cause a ventricle with systolic dysfunction—for which chronic hypertension is a risk factor—to fail and result in pulmonary edema. Diastolic dysfunction from a "stiff," often hypertrophied, ventricle resulting from chronic hypertension may lead to intolerance of tachycardia, often seen postoperatively, because of inadequate ventricular filling time, resulting in hypotension and inadequate cardiac output.

Fortunately, postoperative control of the blood pressure is almost always feasible. Essential to this goal is careful and frequent monitoring of this measurement

during the first several days after a surgical procedure, often using an intra-arterial catheter for direct and continuous monitoring and evaluating the patient for possibly reversible contributing causes of the hypertension. Among these are pain and other discomfort, anxiety and fear, hypercarbia, and volume overload.[26] Pain is a particularly important contributor toward postoperative hypertension; newer approaches toward pain management, such as epidural narcotic infusion, may be useful in patients with postoperative pain. If these factors are corrected as much as possible and the patient remains hypertensive, additional pharmacologic intervention will almost certainly achieve normotension. Medical antihypertensive therapy is especially likely to be needed for patients who are hypertensive preoperatively, whether or not the hypertension had been controlled.

A wide range of nonoral medicines is now available for blood pressure management when a patient is not able to use oral agents. Table 1 lists these with suggested dosing ranges. The drug of choice for a specific patient depends on that patient's circumstances. Often, if the patient has been effectively treated with antihypertensive medicine preoperatively, a parenteral or cutaneous form of that agent will be effective. Other concurrent problems may suggest the use of particular agents: If a patient is also volume overloaded, administering parenteral furosemide may treat both conditions; tachycardia and hypertension may both respond to an intravenous β-blocker[27]; patients with hypertension and heart failure may have both conditions improved with intravenous angiotensin-converting enzyme inhibition; anxious patients with hypertension may gain some sedation as well as a lowering of their blood pressure with cutaneous clonidine; and patients exhibiting evidence of active myocardial ischemia likely would have lessening of the ischemia directly and indirectly through blood pressure reduction, with the use of intravenous nitroglycerin or a β-blocker. If hypertension is moderately severe to severe, agents that produce predictable rapid control would be preferred, such as intravenous sodium nitroprusside. As the patient regains the ability to tolerate oral intake, nonparenteral agents can again be used.

Hypertension Evaluation

When hypertension is detected during the preoperative evaluation, by measurement or history, attention to two other issues besides control of the blood pressure is important. First, screening needs to be done for evidence of secondary hypertension (generally by further history and chart review). Second, hypertension should be considered as a marker of other cardiovascular disease.

Although secondary hypertension is uncommon, some forms can have serious implications for safe perioperative management of the patient. Pheochromocytoma, although rare, can produce disastrous complications during a surgical procedure.[28,29] Pharmacologic and physical stimuli of a patient during and after anesthesia can induce severe swings in blood pressure that are difficult to control and can lead to myocardial infarction, heart failure, or stroke. Long-term excess catecholamine stimulation usually produces a vasoconstriction hypovolemia that may be difficult to detect and seriously complicate proper management of perioperative fluids. If pheochromocytoma is suspected, nonemergent surgical therapy should be delayed until it is known whether the condition is present; if present, such surgical procedures should not be done until the pheochromocytoma preferably is resected or at least its effects optimally blocked by long-term α- and β-adrenergic blockade and volume repletion. For truly emergent operations, immediate aggressive adrenergic blockade is necessary, knowing that the difficulties with blood pressure control are likely to be incompletely prevented.

Patients with Cushing's disease may have problems with postoperative healing and glucose intolerance and a tendency toward hypokalemia. Patients with primary hyperaldosteronism characteristically have hypokalemia that may predispose them to postoperative arrhythmias or weakness. Those with nephropathy may have deterioration of renal function after the stress of a surgical procedure or protein wasting with attendant postoperative nutritional difficulties. Coarctation of the aorta produces hypertension in the upper extremities where the blood pressure is usually measured, whereas lower body blood pressure, including that sensed by the kidneys, remains low, causing possible blood pressure regulation difficulties during and after an operation.

Hypertension is a risk factor for the development of cardiovascular disease, including coronary atherosclerosis (with resulting myocardial ischemia or infarction) and cardiomyopathy (producing heart failure). Although the adverse operative and postoperative effects of hypertension itself can be mitigated by diligent hemodynamic management, these diseases associated with hypertension are clear risks for postoperative cardiovascular events.[30] Every patient found to have hypertension should undergo especially careful questioning for a history or symptoms of these disorders and have close attention paid to the electrocardiogram for evidence of ischemic heart disease. Although many investigators have not found chronic stable angina to increase the risk of perioperative cardiac events, recent myocardial infarction, evidence of heart failure, and nonsinus rhythm or frequent premature ventricular contractions did. Cases of new or increasing angina were not evaluated, but logic dictates that patients with such symptoms would be at increased risk, and unstable angina has been associated with postoperative cardiac morbidity.[6]

It is important to elicit the cardiac history carefully, as many patients, because of denial or a misperception, will not volunteer symptoms. Symptoms often develop so gradually in patients with heart failure that they fail to recognize increasing limitations, or they ascribe them to other causes such as "getting older." Those with angina may think of their symptom as "heartburn" or "chest pressure" and not answer affirmatively when asked if they have chest pain. In addition, angina may well be felt only as discomfort in locations other than the chest, such

TABLE 1.—*Parenteral Drugs for Treating Hypertension**

Drug	*Trade Name†*	*Initial Dose*	*Maintenance Dose*
Propranolol HCl	Inderal	1 to 3 mg IV (1 mg/min); may repeat after several min	Repeat effective dose as needed
Metoprolol tartrate	Lopressor	5-mg boluses IV at 2-min intervals until effect	Repeat effective dose as needed
Esmolol HCl	Brevibloc	500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 min IV, then 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$; repeat boluses and increase maintenance dose by 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 5-min intervals until effect	Continue effective infusion rate, adjust as needed
Labetalol HCl	Normodyne	20 mg IV over 2 min, followed by 40 to 80 mg at 10-min intervals until response *or* 2 mg/min IV infusion	As needed
Clonidine HCl	Catapres	About usual daily dose cutaneously; increase if needed	Change patch(es) weekly
Nifedipine	Procardia Adalat	1/2 to 1 capsule contents sublingually	Repeat as needed
Diltiazem	Cardizem	0.3 to 0.5 mg/kg IV over 2 to 3 min	10 to 15 mg/hr
Verapamil HCl	Calan Isoptin	2.5 to 10 mg IV slow push	Repeat as needed
Enalaprilat	Vasotec	1.25 mg IV over 5 min	Repeat every 6 hr IV
Hydralazine HCl	Apresoline	20 to 40 mg IM or IV	Repeat as needed
Methyldopa	Aldomet	250 to 500 mg IV (effect delayed by hours)	Repeat every 6 hr IV
Furosemide		20 to 40 mg IV	Repeat as needed

HCl = hydrochloride, IM = intramuscularly, IV = intravenously

*The doses given in this table are approximate and should only be used as guides. Not all of the agents listed have been approved by the US Food and Drug Administration for treating hypertension.

†The trade names given are not necessarily inclusive. Their use in this table is informational only and does not represent endorsement by the author or *The Western Journal of Medicine*.

as an arm or the neck, and be easily missed when questions are asked about chest discomfort. The preoperative electrocardiogram must be evaluated not only for arrhythmias, but also for evidence of unrecognized myocardial infarction, which occurs in about a third of cases of infarction.[31] If any evidence of angina that is other than mild and stable, recent myocardial infarction, heart failure, or notable arrhythmias is found, an operation should be delayed if possible until these conditions are further evaluated and optimally treated. Vascular operations require particular caution.[32,33]

Conclusion

Patients with mild or moderate hypertension undergoing surgical procedures pose a risk of having increased blood pressure instability during anesthesia and ischemic complications postoperatively. This risk can be reduced by preoperative and postoperative medication, including continuing a patient's ongoing antihypertensive therapy until the time of an operation, then resuming it as soon as possible postoperatively, including the nonoral forms. The highest risk of cardiovascular complications occurring is during the first several days after an operation. With careful monitoring, the development of hypertension can be detected early during this period and treated with one or more of the many parenteral or cutaneous agents available, as listed in Table 1, individually tailored to a patient's circumstances. The preoperative evaluation of a patient with hypertension should include consideration of the possible presence of secondary hypertension and of hypertension as a marker for cardiovascular disease. By following these principles—in essence, viewing hypertension as a marker for possible hemodynamic instability and cardiovascular complications that can be ameliorated by careful monitoring and appropriate therapy—a patient with hypertension should in most instances be guided safely through the operative and perioperative period.

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Articles

Review of Hepatic Abscess From *Klebsiella pneumoniae*

An Association With Diabetes Mellitus and Septic Endophthalmitis

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I present the only comprehensive review of hepatic abscess from *Klebsiella pneumoniae*. The world literature contains 46 individually reported cases and 3 large studies of *K pneumoniae* liver abscess. The source of the abscesses frequently was not found. Diabetes mellitus was a frequent underlying condition and may predispose patients to the development of liver abscess with this organism. The exact mechanism is unclear, and further investigation is necessary. In addition, extrahepatic metastases, such as septic endophthalmitis, often occurred with serious complications, particularly in patients with diabetes. The association between *K pneumoniae* liver abscess and diabetes is so close that a search for underlying diabetes mellitus is warranted in all patients with *K pneumoniae* liver abscess. Fortunately, earlier diagnoses and better treatment modalities have improved the outcome for these patients.

(Han SHB: Review of hepatic abscess from *Klebsiella pneumoniae*—An association with diabetes mellitus and septic endophthalmitis. West J Med 1995; 162:220-224)

Pyogenic liver abscess from *Klebsiella pneumoniae* is a rare occurrence, with 46 individual cases in addition to three large studies being reported in the international literature.[1-15]

The incidence of *K pneumoniae* liver abscess is increasing, however.[16] During the period from 1960 to 1978, there were fewer than five reports of liver abscess due solely to *K pneumoniae*. Since then, new cases have been reported, with the incidence varying among studies, ranging from 40% to 51% of all pyogenic liver abscesses, including those diagnosed by both pure and mixed cultures.[9,16] The highest incidence of *K pneumoniae* liver abscess is reported in Asia, where it is a leading cause of pyogenic liver abscess in Taiwan.[14]

The increased incidence of *K pneumoniae* liver abscesses may parallel the recent increase in the incidence of liver abscesses due to gram-negative rods.[17,18] The reason for this latter increase remains unclear, but it has been speculated that these organisms may be arising more often as a result of the widespread use of antibiotics or the increased incidence of hospital-acquired infections.[19] *Escherichia coli* remains the most frequently identified gram-negative organism, followed by *Klebsiella*, *Proteus*, and *Pseudomonas* species.[17]

Clinical Characteristics

The characteristics of the patients with *K pneumoniae* liver abscess are summarized in Table 1.[1-15] Their ages range from 28 to 87 years, except for one case of a 37-week-old infant in whom *K pneumoniae* liver abscess developed from a procedural complication.[2] This is consistent with the observation that pyogenic liver abscess is predominantly a disease of middle-aged to older patients.[20] In most patients, the abscesses were located predominantly in the right hepatic lobe, perhaps a result of its larger size and blood flow. The size of the abscesses ranged from 4 to 15 cm. In at least 62% of patients, the abscesses were solitary. Solitary abscesses often present insidiously.[19,21] In most of the reported cases, *K pneumoniae* was cultured from both the liver aspirate and the blood. In cases where cultures were positive from only one source, the organism was more frequently isolated from the liver aspirate. For pyogenic liver abscess, culture positivity with the causative organism falls in a range between 33% and 66% for the blood and between 73% and 100% for the liver aspirate. When both the blood and aspirate cultures are positive, they will often be positive for the same organism.[20] The cultures reported in this review of the literature grew only *K pneumoniae* unless otherwise stated (Table 1).

The source of the liver abscess was neither found nor mentioned in most cases reported. In fact, possible sources of liver abscesses were alluded to in only two of the cases.[2,10] For pyogenic liver abscesses in general, no source is found in 50% to 75% of solitary abscesses.[21,22] Possible sources reported include biliary tract disease (cholelithiasis, cholangitis, cholecystitis), followed by portal venous disease (diverticulitis, inflammatory

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TABLE 1.—*A Summary of the Literature on* Klebsiella pneumoniae *Liver Abscess*

Source	Patients No.	Patients Sex	Patients Age	Underlying Condition	Liver Abscess Location, Lobe	Liver Abscess Size, cm	Liver Abscess No.	Cultures Blood (K pneumoniae)*	Cultures Liver (K pneumoniae)*	Other Sites	Complications or Outcome
Di Figlia and Cramer, 1951[1] ...	1	F	55	Diabetes mellitus	Right	5	4	(+)	NA	CSF	Died
Fraga et al, 1974[2].....	2	F	37†	None	NA	NA	1	(+)	NA	CSF, umbilical vein	Sepsis, died
Goldman and Kowalec, 1978[3]...	3	M	48	None	Right	9	1	(−)	(+)	Tibia	Survived
Salky et al, 1982[4].....	4	F	68	Diabetes, hypertension, seizures, CHF	Left	NA	3	(+) *Streptococcus faecalis*	(+)	NA	Pneumoperitoneum
Chew et al, 1985[5].....	5	F	70	Diabetes, hypertension, asthma peptic ulcer, hypothyroidism	Left, right	10, 4	1	(−) Group D Strep	(+)	Skin	Survived
.....	6	F	36	Diabetes, hepatitis B,	Left, right	10	1	(+)	(+)	NA	Survived
.....	7	M	37	Diabetes, hepatitis B	Right, left	8/4	2	(−)	(+) *Escherichia coli*	Peritoneum	Survived
.....	8	F	75	Diabetes, cholecystectomy	Left	4	1	(+)	(+)	NA	Died
Liu et al, 1986[6].....	9	M	55	Diabetes	Left	NA	NA	NA	(+)	Left eye	Enucleation
.....	10	F	64	None	Right	NA	1	(+)	(−)	Left eye, lungs	Survived
.....	11	M	29	None	Right	8	1	(+)	(+)	Right eye, lungs	Survived
.....	12	M	37	Diabetes	Right	4	1	(+)	NA	Right eye, lungs	Enucleation
.....	13	M	60	Diabetes	Right	NA	1	(+)	NA	Right eye, prostate, lungs	Enucleation
.....	14	M	75	Diabetes	Right	NA	1	(+)	(+)	Left eye	Enucleation
.....	15	M	77	None	Right	5	1	(+)	(+)	Right eye, CSF	Survived
Chang et al, 1988[7].....	30 pts (18M, 12F)			Diabetes in 16, cholelithiasis in 7	Right in 22, left in 5, both in 3	>5	‡	(+) (n = 17)	(+) (n = 27)	Eye (1), skin (1), lungs (1)	3 Died
Chiu et al, 1988[8].....	58/180			Cholelithiasis in 62, diabetes in 34	NA	NA	NA	(+) (n = 41)	NA	Eye in 3:	NA
.....	16	F	74	Diabetes	NA	NA	NA	(+)	(+)	Eye	Enucleation
.....	17	M	46	Diabetes	Right	4	1	(+)	(+)	Left eye	Blindness
.....	18	M	75	Cholelithiasis	NA	NA	NA	(+)	(+)	Eye	Blindness
Cheng et al, 1989[9].....	89/175			Diabetes in 71 (40.6%), cholelithiasis in 48	NA	NA	NA	(+) n = 47	(+) n = 78	NA	NA
Casanova et al, 1989[10]	19	NA	55	None	NA	10	1	(+)	(+)	Left eye	Enucleation
Ridker et al, 1989[11]	20	M	33	None	Right	9	1	NA	(+)	NA	Positive Monospot test

(continued on next page)

Table 1 continued from previous page

Source	Patients No.	Patients Sex	Patients Age	Underlying Condition	Liver Abscess Location, Lobe	Liver Abscess Size, cm	Liver Abscess No.	Cultures Blood (K pneumoniae)*	Cultures Liver (K pneumoniae)*	Other Sites	Complications or Outcome
Yanagawa et al, 1989[12]	21	M	53	Diabetes	NA	NA	1	(+)	NA	CSF	NA
Barton et al, 1991[13]	22	M	37	Diabetes	NA	NA	1	(+)	(+)	NA	Died
.....	23	M	45	Diabetes	Right	NA	1	(+)	(+)	NA	Died
.....	24	M	47	Diabetes, hypertension	Right	NA	1	(+)	(+)	NA	Died
.....	25	M	42	Diabetes	Left	NA	2	(+)	(+)	NA	Survived
.....	26	M	55	Diabetes	NA	NA	1	(+)	(+)	NA	Died
Cheng et al, 1991[14]	27	M	55	Diabetes	NA	NA	NA	(+)	(+)	Left eye	Blindness
.....	28	M	61	Diabetes, cholelithiasis	NA	NA	NA	(+)	(+)	Lungs, CSF	Survived
.....	29	F	64	None	NA	NA	NA	(+)	(−)	Left eye, lungs	Blindness
.....	30	M	28	None	NA	NA	NA	(+)	(+)	Right eye	Partial blindness
.....	31	M	37	Diabetes	NA	NA	NA	(+)	NA	Right eye, lungs	Blindness
.....	32	M	65	Diabetes	NA	NA	NA	(+)	(+)	Lungs	Survived
.....	33	M	60	Diabetes	NA	NA	NA	(+) *E coli*	NA	Right eye, lungs, prostate	Blindness
.....	34	M	74	Diabetes	NA	NA	NA	(+)	(+)	Left eye	Blindness
.....	35	M	77	None	NA	NA	NA	(+)	(+)	Left eye, lungs, CSF, kidneys	Blindness
.....	36	M	68	Diabetes	NA	NA	NA	(+)	NA	Kidneys	Survived
.....	37	M	61	None	NA	NA	NA	(+)	(+)	Both eyes, CSF	Blindness
.....	38	M	64	Diabetes	NA	NA	NA	(+)	(+)	Bone, psoas abscess	Survived
.....	39	M	61	Diabetes	NA	NA	NA	(+)	(+)	Both eyes, CSF	Died
.....	40	M	31	Diabetes	NA	NA	NA	(+)	(+)	Bone	Survived
.....	41	M	59	Diabetes, cholelithiasis	NA	NA	NA	(+)	(+)	Left eye, CSF	Coma
.....	42	M	70	NA	NA	NA	NA	(+)	(+)	Kidneys	Survived
.....	43	M	33	Diabetes	NA	NA	NA	(+)	(+)	Lungs, CSF	Survived
.....	44	M	45	Diabetes	NA	NA	NA	(+)	(+)	Left eye	Blindness
.....	45	M	67	None	NA	NA	NA	(2)	(+)	Left eye	Partial blindness
Couez et al, 1991[15]	46	F	56	Hypothyroid	NA	15	1	(−)	(+)	Right eye	Blindness

CHF = congestive heart failure, CSF = cerebrospinal fluid, NA = not available, Strep = streptococcus

*A plus sign in parentheses means a culture was positive for *K pneumoniae*; a minus sign in parentheses means a culture was negative for *K pneumoniae*.
†Age is given in weeks.
‡In 27 cases, the abscess was a solitary one.

bowel disease, appendicitis), contiguous spread (trauma or postoperative), and hematogenous spread (pneumonia, endocarditis, osteomyelitis, otitis media).[7,20,23]

In this review, the most common presenting signs and symptoms were nonspecific and included fever, chills, abdominal tenderness, and hepatomegaly. The most frequent laboratory abnormalities were an increased alkaline phosphatase level, decreased albumin value, increased aminotransferase levels, and an elevated leukocyte count. These findings are not specific for *K pneumoniae* liver abscess, but are seen with pyogenic liver abscesses due to other organisms, including amebic abscesses.[17,18,20-23]

Underlying Medical Conditions

With the increased incidence of gram-negative liver abscesses, the possible association between pyogenic liver abscess and certain medical conditions has been uncovered. Although a relationship between pyogenic liver abscess and diabetes has not been proved, it has been suggested that persons with diabetes have a defect in their host-defense mechanisms that makes them more susceptible to the development of pyogenic liver abscess.[7] Furthermore, because persons with diabetes are prone to the development of gram-negative sepsis, organisms such as *E coli* and *K pneumoniae* would tend to emerge.[5] In two of the reports,[8,9] the percentage of patients with pyogenic liver abscess having diabetes was 41% (71/175) and 19% (34/180), respectively, but the reports did not give the percentages of those with *K pneumoniae* liver abscess and diabetes. Cheng and colleagues did comment that the high incidence of *K pneumoniae* liver abscess in their series, the second highest reported, was due to the large number of patients with diabetes mellitus in their study.[9] In another report, diabetes was found to be the most commonly associated disease in patients with *K pneumoniae* liver abscess, occurring in 16 patients (53%) in that series.[7]

In this review of 46 cases, 30 patients (65%) had diabetes, the most common underlying condition. Biliary tract disease, although the next most common underlying condition, was far less frequent, occurring in 4 patients (9%) reported here. Therefore, the data do suggest that diabetes mellitus may predispose to *K pneumoniae* liver abscess.

Extrahepatic metastases developed in many of the patients with *K pneumoniae* liver abscess, resulting in some serious complications. The most worrisome complication involved the eyes. In this review of the literature, 25 patients had septic endophthalmitis (Table 1).[6-8,10,14,15] This ophthalmic complication has an extremely poor prognosis, and blindness or enucleation of the affected eye is the usual result.[6,10] Septic endophthalmitis in patients with liver abscess due to gram-negative organisms other than *K pneumoniae* is associated with a poor outcome, but *K pneumoniae* appears to be particularly virulent when associated with septic endophthalmitis.[8] The propensity for septic metastases, such as endophthalmitis, to develop in patients with diabetes may be due to these patients' proclivity for bacteremia.[14]

Of the 46 reported cases in Table 1, 23 of the 37 patients (62%) with extrahepatic metastases in this review had diabetes mellitus as an underlying condition, and of the 25 patients in whom septic endophthalmitis developed, 13 (52%) had diabetes. Hence, although diabetes is not essential for the development of septic metastases in patients with *K pneumoniae* liver abscess, the high percentage of patients with diabetes suggests that this disease contributes to the chance of metastases developing. Other extrahepatic sites reported include the skin, kidneys, lungs, bones, prostate, muscle, and cerebrospinal fluid (Table 1). Involvement of the cerebrospinal fluid is associated with a poor prognosis.

Pyogenic liver abscess had a uniformly high mortality many years ago, but advances in diagnosis and treatment have resulted in a better outcome for this disease. Earlier diagnosis of pyogenic liver abscess is now possible with the newer, noninvasive techniques available.[20] *Klebsiella pneumoniae* liver abscess was diagnosed by ultrasonogram in 83 (93%) of 89 patients in one study (sensitivity, 85% to 95%).[9] Ultrasound best distinguishes cystic from solid structures.[23] Abdominal computed tomographic scans are also highly sensitive (95%) in diagnosing liver abscess and offer the advantage over ultrasonography that they better identify possible abdominal sources of liver abscess such as diverticulitis or appendicitis.[23]

Management

A liver abscess can be percutaneously drained under both ultrasonographic and computed tomographic guidance. Liver abscesses are still drained surgically, but more recently, percutaneous aspiration and drainage has become the preferred procedure in their management.[15,21,23] Surgical drainage should be considered if a patient fails to improve at a satisfactory rate with percutaneous drainage and antibiotics, the presence of multiple abscesses renders percutaneous drainage technically difficult, or additional problems are present that may be treated surgically such as bile duct obstruction or diverticular or appendiceal disease.[24] The length of time to keep a catheter in place remains undefined. Some authors advocate keeping the catheter in place until the drainage has ceased,[23] but others question the value of prolonged catheter drainage versus one-time needle aspiration.[24]

When awaiting culture results, the parenteral antibiotic treatment of *K pneumoniae* liver abscess should be broad-spectrum coverage to include other enteric gram-negative organisms. Anaerobic coverage should also be instituted because anaerobic organisms are present in half of all patients with liver abscess.[24] The duration of antibiotic treatment of *K pneumoniae* liver abscess varies from two to four weeks for a solitary abscess and as long as six weeks for multiple abscesses,[7] although the proper duration is undefined. Some authors advise continuing parenteral antibiotics for five to seven days after leukocytosis and fever resolve.[24] Earlier diagnosis and improved treatment modalities have notably reduced the mean length of a hospital stay for this disease.

In summary, the close association between *K pneumoniae* liver abscess and diabetes mellitus should warrant an evaluation for underlying diabetes in any patient presenting with *K pneumoniae* liver abscess. Physicians should recognize the potential for extrahepatic septic metastases and their complications. Prompt drainage and antibiotic treatment will improve the chance of a favorable result.

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Articles

Methotrexate Therapy
Nonsurgical Management of Ectopic Pregnancy

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Ectopic pregnancy has become a surgical epidemic over the past two decades. To minimize the morbidity, mortality, and financial burden created by this rapidly growing health problem, nonsurgical alternatives have been investigated, including treatment with methotrexate. We reviewed current literature to evaluate the safety, efficacy, and costs associated with methotrexate treatment of tubal pregnancy. To date, 17 studies have reported on 400 patients with tubal pregnancies treated with parenteral methotrexate; the overall success rate was 92% (95% confidence interval, 89% to 95%). Single-dose parenteral methotrexate has been shown to be safe, effective, and associated with minimal costs when used in carefully selected patients. A prospective, randomized clinical trial comparing medical and surgical management of ectopic pregnancy is needed to assess the risks, benefits, and costs of these two approaches.

(Slaughter JL, Grimes DA: Methotrexate therapy—Nonsurgical management of ectopic pregnancy. West J Med 1995; 162:225-228)

The incidence of ectopic pregnancy has reached epidemic proportions in the United States. In 1989, a total of 88,400 cases of ectopic pregnancy were reported, accounting for 1.6% of all pregnancies.[1]

The increasing frequency of this disorder is of particular concern because of associated morbidity and mortality: ectopic pregnancy causes 13% of all pregnancy-related deaths and is the leading cause of maternal death in African-American women.[1] Implications for future fertility are similarly grim: the conception rate overall is 60% after ectopic pregnancy, with rates of 20% for recurrent ectopic pregnancy, 30% for spontaneous abortion, and only 30% for subsequent live birth.[2] In addition, the financial burden of ectopic pregnancy in the United States is substantial, with an estimated cost of $1.1 billion in 1990 alone.[3] This figure includes only hospital charges and lost wages, with no account of the cost of subsequent morbidity.

In the past, ectopic pregnancy has been treated surgically. Cases of ectopic pregnancy were diagnosed late, often after rupture. Laparotomy with salpingectomy was the treatment of choice. Currently, salpingectomy is required only in women with tubal rupture, anatomic distortion, or overt hemorrhage[4] because ectopic pregnancies can be diagnosed much earlier through the use of sensitive β-human chorionic gonadotropin (β-hCG) assays and transvaginal ultrasonograms. Cases diagnosed at an earlier stage are amenable to more conservative methods of treatment, such as laparoscopic salpingotomy or salpingostomy. These procedures can be done safely and efficiently for patients with unruptured ectopic pregnancies of less than 5 cm in greatest diameter.[4] Of conservative operations, however, 3% to 20% result in persistent viable trophoblastic tissue requiring additional surgical or medical treatment.[5]

The most widely studied nonsurgical therapy to date is management with methotrexate. This folinic acid antagonist inhibits dihydrofolate reductase activity, preventing synthesis of amino acids, RNA, and DNA. Methotrexate targets rapidly dividing cells, including fetus and trophoblast, bone marrow, buccal and intestinal mucosa, and malignant cells. Methotrexate has been used since 1956 for gestational trophoblastic disease.[6] Its repeated use is limited by dose- and duration-dependent side effects: severe leukopenia, bone marrow aplasia, thrombocytopenia, ulcerative stomatitis, diarrhea, liver cell necrosis, hemorrhagic enteritis, and even death from intestinal perforation.[7] Severe side effects can be prevented by following a lethal dose of methotrexate with reduced folate (leucovorin calcium [citrovorum factor]) to rescue surviving cells. In contrast, single-dose administration has few side effects.[8]

Methods

We reviewed the English-language literature on methotrexate therapy for ectopic pregnancy by conducting a MEDLINE search using key words "ectopic pregnancy" and "methotrexate" and found 113 articles.

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Adding the key word "fertility" narrowed the list to 17 articles. A search including the key word "cost" yielded no more citations. Our search was supplemented by reference lists from original research, review articles, and textbooks. We also consulted authorities in the field of ectopic pregnancy and health care policy. We used tables of binomial distribution[9] and computer software to calculate 95% confidence intervals for series reports of parenteral methotrexate therapy for tubal ectopic pregnancy and overall success rates.

Results

Beginning in 1963, methotrexate was used to treat ectopic pregnancies in patients with high surgical risk such as those with abdominal pregnancy with a bulky placenta attached to omentum and bowel[10] and interstitial[11] and cervical[12] pregnancies, with varying success rates.

Methotrexate treatment of ectopic pregnancy is successful in 67% to 100% of selected patients (Table 1).[11,13-29] In 1986, an eight-day regimen of intravenous methotrexate, alternating daily with intramuscular leucovorin calcium, was used in six patients with tubal ectopic pregnancy, and five of six (83%) pregnancies resolved.[17] These results were confirmed in subsequent studies.[18,20,21] During this time, medical management of ectopic pregnancy was conducted in the context of diagnosis by laparoscopy. In 1990 a prospective, randomized trial of an algorithm without laparoscopy was used that proved to be 100% accurate in diagnosing tubal pregnancies.[30] This made possible completely nonsurgical management of tubal pregnancy. In 1991, in the first of two studies, an expanded group of 100 patients received a standard methotrexate and leucovorin regimen, with a 96% success rate.[25] Of these patients, 64 subsequently conceived, with 89 intrauterine and 11 recurrent ectopic pregnancies. Of the 100 patients, 5 had methotrexate-related side effects.

In the second study, 30 patients were given a single dose of 50 mg per m^2 of methotrexate intramuscularly, without leucovorin calcium rescue.[8] Of the 30 patients, 29 (97%) were successfully treated; no methotrexate side effects were reported. Of the 30 patients, 6 (20%) had increased lower abdominal pain on days 5 to 10 after treatment, however.[8] This complication of methotrexate treatment would be disturbing in an outpatient with an ectopic pregnancy who must be closely monitored for possible rupture.

In 1993 a series of 120 patients were given methotrexate intramuscularly, with 113 (94%) being successfully treated[29]; no side effects occurred. The mean time to resolution of the ectopic pregnancy was 35.5 ± 11.8 days, with a range of 8 to 76 days until the β-hCG titer was less than 12 IU per liter (12 mIU per ml). After methotrexate therapy, 80% of patients conceived within a mean interval of 3.2 ± 1.1 months. Of these conceptions, 87% were intrauterine, and 13% were ectopic.[29]

To date, 17 studies have reported on 400 patients with tubal pregnancies treated with parenteral methotrexate; the overall success rate was 92% (95% confidence interval, 89% to 95%). Strict criteria are required for methotrexate treatment (Table 2). The most important selection criteria for medical management are the absence of pain and the prediction that the pregnancy will not rupture before its resolution.[31] Fetal cardiac activity was considered to be a relative contraindication because the failure rate in the presence of cardiac activity (2 of 14, 14%) was higher than the failure rate in the absence of cardiac activity (5 of 106, 5%; $P < .05$) (Table 3).[29] Two cases were reported of failed methotrexate therapy (local and parenteral administration) in women with tubal pregnancy in which there was fetal heart rate activity, however.[32]

TABLE 1.—*Case Series of Parenteral Methotrexate Therapy in Tubal Pregnancy*

Study	Treatment*	Patients, No. (n = 400)	Success Rate, %	95% CI, %
Tanaka et al, 1986[11]	A1	1	100	2-100
Miyazaki et al, 1983[13]	A2	8	88	47-100
Chotiner, 1985[14]	A3	1	100	2-100
Brandes et al, 1986[15]	A4, C	1	100	2-100
Goldstein, 1986[16]	A4	7	92	64-100
	D	6		
Ory et al, 1986[17]	B1, C	6	83	36-100
Rodi et al, 1986[18]	B3, C	7	100	59-100
Haans et al, 1987[19]	B4	1	100	2-100
Ichinoe et al, 1987[20]	A6	23	96	78-100
Sauer et al, 1987[21]	B3, C	21	95	76-100
Sauer et al, 1988[22]	B3, C	4	100	40-100
Carson et al, 1989[23]	A4, C	21	90	70-99
Stovall et al, 1989[24]	A5, C	36	94	81-99
Stovall et al, 1991[25]	B3, C	100	96	90-99
8yrjalsen and Toft, 1991[26]	A6	9	67	30-93
Isaacs et al, 1992[27]	B2	8	100	63-100
Prapas et al, 1992[28]	B3, C	20	95	75-100
Stovall and Ling, 1993[29]	A7	120	94	88-98
Total			92	89-95

CI = confidence interval

*Treatment methods:
A1 = methotrexate, 30 mg given intramuscularly (IM), then 15 mg for 5 days × 3 courses.
A2 = methotrexate, 60-300 mg IM; dose based on initial urine human chorionic gonadotropin (hCG) titer.
A3 = methotrexate, 25 mg IM daily for 3 days; 20 mg IM daily for 7 days.
A4 = methotrexate, 1 mg/kg IM for 4 days.
A5 = methotrexate, 1 mg/kg IM for 5 days.
A6 = methotrexate, 0.4 mg/kg IM for 5 days every other week: 60-300 mg total dose based on initial urine hCG titer.
A7 = methotrexate, 50 mg/m^2 IM, single dose.
B1 = methotrexate, 1 mg/kg given intravenously (IV) for 4 alternating days.
B2 = methotrexate, 1 mg/kg IM for 3 alternating days.
B3 = methotrexate, 1 mg/kg IM for 4 alternating days.
B4 = methotrexate, 50 mg IM for 4 alternating days with 15 mg of folic acid taken orally.
C = leucovorin calcium (citrovorum factor), 0.1 mg/kg IM on alternate days.
D = methotrexate, 200 mg/m^2 IV.

Discussion

Single-dose methotrexate therapy has been shown to be as effective as the multidose regimen, but with a smaller total dose of methotrexate, no need for leuco-

TABLE 2.—*Criteria for Methotrexate Therapy*

Stovall and Ling, 1993*
Hemodynamically stable
hCG titers increased after curettage
Transvaginal ultrasonography showed an unruptured ectopic pregnancy < 3.5 cm in greatest diameter
Desire for future fertility
American College of Obstetricians and Gynecologists, 1990†
Ectopic size 3 cm or less
Desire for future fertility
Stable or rising hCG levels with peak values < 15×10^3 IU/liter (15,000 mIU/ml)‡
Tubal serosa intact
No active bleeding
Ectopic pregnancy fully visible at laparoscopy
Selected cases of cervical and cornual pregnancy

hCG = human chorionic gonadotropin

*From Stovall and Ling.[29]
†From ACOG.[4]
‡International Reference Preparation.

TABLE 3.—*Contraindications to Methotrexate Therapy*

Stovall and Ling, 1993*
Hepatic dysfunction: aspartate aminotransferase level > 2 × normal
Renal disease: serum creatinine level > 130 μmol/liter (1.5 mg/dl)
Active peptic ulcer disease
Blood dyscrasia: leukocyte count < 3.0×10^9/liter (3,000 cells/mm^3) or platelet count < 100×10^9/liter (100,000/mm^3)
American College of Obstetricians and Gynecologists, 1990†
Contraindications listed above, plus
Poor patient compliance
History of active hepatic or renal disease
Presence of fetal cardiac activity

*From Stovall and Ling.[29]
†From ACOG.[4]

vorin, decreased patient hospital stays, fewer side effects, and lower costs. The single-dose regimen can be given on an outpatient basis, allowing women to return to work during treatment. This compares favorably with the four- to six-week delay in return to work after laparotomy and one- to two-week delay after laparoscopy.[3] In addition, methotrexate therapy is associated with high rates of subsequent fertility: as high as 80% in one population, with most of these intrauterine.[25] The disadvantages of single-dose parenteral methotrexate include prolonged time for an ectopic pregnancy to resolve: as long as 70 to 120 days. Outpatients must be closely monitored for rupture and methotrexate side effects, making compliance an important consideration in patient selection.

Finally, the costs of different methods of managing ectopic pregnancy must be considered. In 1993, the costs of methotrexate treatment of ectopic pregnancy were compared with those of surgical methods.[3] If all eligible patients nationwide had received single-dose methotrexate therapy instead of surgical management (about 30% of all cases of ectopic pregnancy seen at San Francisco General Hospital Medical Center in 1991), an estimated 24% to 26% of hospital costs, lost wages, and costs of morbidity could have been saved. The potential annual cost savings exceeds $282 million. This estimate is based on an assumption of 28 days of disability with laparotomy, 7 days with laparoscopy, and 4 days with methotrexate therapy.[3]

Administering methotrexate appears to be a promising approach to managing ectopic pregnancies. Although it cannot be used for every patient, it offers a safe and effective nonsurgical method of treating selected patients. A randomized controlled trial comparing methotrexate treatment with surgical management is needed to define the appropriate role of methotrexate therapy for ectopic pregnancy.

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* * *

PEOPLE WHO LIVE IN GLASS HOUSES

An old man sitting up front in a hard chair, in a tattered blue robe,
with legs crossed, was asked by the psychiatry resident,
"Do you know what to kill two birds with one stone means?"

Certainly, he said. If you were walking next to me on 42nd Street
and a hoodlum ran by to steal your wallet he could put a knife in your ribs,
and twist it until the blade broke off and you could fall on me, your blood
pouring in my mouth, suffocating me, the collar of your coat stretched
across my neck, and what good would it do to yell, I've been here

before, it's not a memory lapse. I could tell you what Jimmy Walker said
when he was mayor and you'd wonder if I made it up or why they put me here
when I was twenty-five. But that was the beginning of the depression.
It was possible to stay a while, avoid the breadlines and when it was over
why go to World War II when here there was three squares and a bed,
and after that the outside seemed bleak; people never realize it
when young like you. So you sit there casually, but nervous,

stethoscope showing from a side pocket, asking me
in front of sixty students this question, hoping I give you
a concrete rather than abstract answer. There are no metaphors

here. There are the same hallways, the same room,
same robe every day. But while I think about it,
what does it mean to you, people who live
in glass houses shouldn't throw stones?

MARC STRAUS, MD©
Chappaqua, New York

Articles

Making the Health Care System 'Safe' for Persons With HIV Infection or AIDS

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If health care reform is implemented in states and nationally, the safety of this process needs to be examined for persons with human immunodeficiency virus (HIV) infection or the acquired immunodeficiency syndrome (AIDS). Reform should assure ongoing prevention and transmission control of HIV and continuous coverage of medical costs for persons ill with HIV or AIDS. These persons currently benefit from various state and federal categoric programs designed to assure access to preventive and personal care services.

Washington State has passed health care reform legislation that envisions integrating these programs to provide a system of population-based and personal health care. This legislation was analyzed using existing epidemiologic and entitlement information about persons with HIV infection or AIDS in the state to assess its effect.

The relationship between public health and personal care services will be a central concern for those with HIV infection or AIDS, and complete coverage of this group may be achieved relatively late in the process of implementing health care reform. Health personnel planning under health care reform will affect the delivery of HIV- and AIDS-related services. Including treatment of AIDS in the basic benefit package merits particular attention. These issues parallel those being faced by the nation as a whole as it seeks to ensure epidemic disease control and compassionate care for long-term disabling illness if health care reform is implemented.

(Kimball AM, Lafferty B, Shields A, Smyser M: Making the health care system 'safe' for persons with HIV infection or AIDS. West J Med 1995; 162:229-234)

During the legislative session of 1993, Washington State joined a number of other states—including Oregon, Massachusetts, Hawaii, and Minnesota—in leading the national effort for health system reform. Senate Bill 5304, "Engrossed Second Substitute" bill, includes a wide range of provisions for universal insurance coverage, malpractice reform, statewide public health, resource planning, and revenue generation.

Persons with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) have been among the groups most affected by the shortcomings of the present health care system in the United States—narrow coverage, exclusion clauses for preexisting conditions, and limited coverage for prescription drugs. As the AIDS epidemic moves into its second decade of continued HIV transmission, care for persons with HIV has become a financial "hot potato." Private insurers, state governments, and the federal government have been reluctant to shoulder this open-ended and ever-increasing financial obligation. In 1992, for example, Medicare paid 40% of the cost of AIDS care nationally—an arresting example of "finance defaulting." Simultaneously, a variety of categoric programs have been put in place under private funding and grants from the Centers for Disease Control and Prevention (CDC) for preventive efforts.

With the possibility of health care reform still on the horizon, how to incorporate HIV and AIDS programs into a universal coverage scheme remains a question. How can "safe" health care reform for this group—continuous coverage, access to appropriate services, and the continuation of preventive services—be assured? We examine these issues from the perspective of a state health department.

In general, state resources are stretched thin; many states are running large deficits, and pressure is mounting to decrease public spending in all areas of government. The deficit for Washington State in 1993 was esti-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control and Prevention
HIV = human immunodeficiency virus

mated to exceed $1 billion, which caused substantial reductions in spending to ensure the balanced budget mandated by law.

State government cannot afford to leave vulnerable groups without coverage during the process of health care reform, nor do they possess the flexibility to duplicate benefits. Detailed and precise planning will be vital to charting the wisest possible course.

We studied the possible effects of health care reform on Washington State residents with HIV infection or AIDS by covering issues found in both state and national level policy and framing the national discussion of health care reform that was in progress at that time.

Materials and Methods

Our preliminary study included the following: reviewing newly passed legislation to identify areas pertinent to the prevention or care of HIV infection or AIDS, reviewing data collected by the State Department of Health in the course of the surveillance of HIV infection or AIDS and surveillance-related special studies, and reviewing data collected by the State Department of Health and the University of Washington on expenditures for the care of persons with AIDS and current health personnel and resource distribution in the state of Washington.

Epidemiologic information included statewide reports of all symptomatic cases of HIV disease (class IV AIDS),[1] seroprevalence studies carried out in collaboration with the CDC,[2] and an in-depth interview project conducted by the Washington State Department of Health and its county health department partners.[3]

We also reviewed entitlements paid through the Washington State HIV Intervention Program and the AIDS Prescription Drug Program supported by Ryan White legislative funding (Ryan White Comprehensive AIDS Resources Emergency [CARE] Act of 1990). Variables examined included the number of persons, number and cost of prescriptions, and average cost of prescriptions. Cost-of-care studies, medically underserved population data, and shortages of health professionals were also considered.

Our review focused on the following areas:

- Who are the people with HIV infection or AIDS in Washington?
- How will prevention and case-management services be affected by health care reform?
- How will the care of these patients be financed?
- What care will they receive under the reformed system?
- Where will they receive care?

Results

Who Are the People With HIV Infection and AIDS in Washington?

A total of 3,252 cases of AIDS were reported in Washington State in 1992. Of those, 1,132 persons were alive in 1993. Men were affected at a rate of 129.7 per 100,000 compared with a rate of 4.93 per 100,000 for women. The rate for African Americans (156 per 100,000) was more than twice that for whites (66.5 per 100,000). An estimated 10,000 to 20,000 Washington State residents are thought to be infected with HIV. As shown in Figure 1, the number of new AIDS cases statewide is projected to hold steady over the next five years, but the cumulative number of cases will continue to increase through the year 2000 (B. L., M. S., C. Maden, H. Thiede, S. Hopkins, N. Harris, "HIV/AIDS Forecast Committee Report for Washington State and King County," Department of Health, unpublished data, May 1993). In 1991 an estimated $37 million was spent on the care of persons with HIV disease in Washington State (B. L., "Increase in Projected Estimates of Cost for HIV/AIDS Care," Office of HIV/AIDS Epidemiology and Evaluation, unpublished data, December 1994).

How Will Prevention and Case Management Services Be Affected by Health Care Reform?

The recently passed legislation requires the state Department of Health to design a public health plan to be presented to the legislature in 1995 for funding. This plan has been drafted and submitted, and the legislature is now considering it. How the overall plan will affect existing categorical programs has therefore not yet been decided. Access, prevention, and case management services for persons with HIV or AIDS could change as reform is implemented.

State-funded categoric public health services for the prevention of HIV transmission are currently mandated through the AIDS Omnibus legislation passed in 1988. This legislation describes a regionalized AIDS Service Network System (AIDSNETS) that combines 39 counties into six regions (Figure 2). State dollars ($8.1 mil-

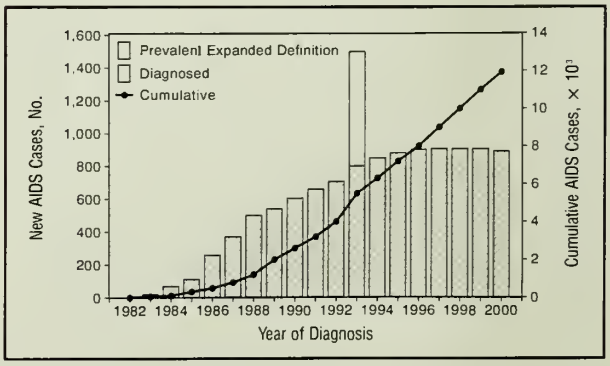

Figure 1.—The graph shows the projected number of AIDS [acquired immunodeficiency syndrome] cases in Washington State to the year 2000.

lion in 1991) are appropriated by the legislature and pass directly to these regional networks for executing programs through a variety of governmental and nongovernmental organizations in each region. Contracting responsibility lies with the county health departments.

Legally mandated prevention services include voluntary and anonymous counseling and testing; mandatory testing for certain groups; notification of sexual partners of those infected; education for the general public, health professionals, and high-risk groups; and related community-outreach services for runaway youth.

Although a newly designed reporting system is now in place to track the performance of activities financed by state funds, data are not yet available. The system does not provide information on population coverage, cost of individual activities, or efficacy.

The public health activities of counseling, testing, and case management and referral represent "intake" points for persons early in HIV illness. Because of concerns about confidentiality, these services have been provided in two ways: publicly funded anonymous counseling through state mechanisms and privately financed testing carried out as part of routine medical care.

In 1992 Washington State publicly funded 49,876 HIV tests. According to a survey by the Department of Health in 1991, however, more than a million Washingtonians have been tested for HIV (Office of Prevention, Education Services, Division of HIV/AIDS, Washington State Department of Health, unpublished data, 1992). This suggests that, despite concerns about confidentiality, extensive testing is occurring in the private sector. Because this information is proprietary, public planners are unable to verify how much testing is being financed by third-party payers. State law dictates that pretest and post-test counseling will occur with any HIV testing; costs are estimated at $70 to $100 per person. Although compliance in the private sector is unclear, counseling and testing costs for the public sector totaled more than $2 million for 1992 (Office of Prevention, Education Services, Division of HIV/AIDS, Washington State Department of Health, unpublished data, 1992).

Under health care reform, health care financing for persons with HIV or AIDS will undoubtedly change. Health insurance coverage for the entire population of Washington State will occur through two mechanisms: an extension of the current basic health plan to additional geographic areas of the state and the implementation of phased, employer-based plans. In the past, the basic health plan has carried a clause denying coverage for preexisting conditions and has not covered drugs, although this was scheduled to change in 1994. To prevent this publicly subsidized plan from covering a disproportionate number of such cases, restrictions on preexisting conditions will remain in place longer for the basic health plan than for other health plans; the retirement of these restrictions is as yet undecided. In January 1994, pharmacy benefits included antiretrovirals as "tier 3" drugs on the formulary and required a 50% copayment by the subscriber. Enrollment in the basic health plan was scheduled to increase from 29,000 in 1992 to 120,000 by the close of 1994. How nearly this target has been met is not clear. No information on diagnostic groups within this population is available—the number of persons with AIDS who will be joining the plan is not known.

Our analysis suggests that in Washington State, persons with HIV infection or AIDS will not be covered within the next few years by the employer-based scheme. Employment status is not routinely collected through disease reporting, but data on employment status were compiled from a research project and two service programs in Washington State (Table 1).

Those being supported in the existing insurance continuation program include at least 251 persons (81% of enrollees) who had lost their employer-based insurance, as indicated by the designated payees for their premium support. Premiums under both the Consolidated Omnibus Budget Reconciliation Act and High-Risk Insurance Pool initially provided that eligible persons

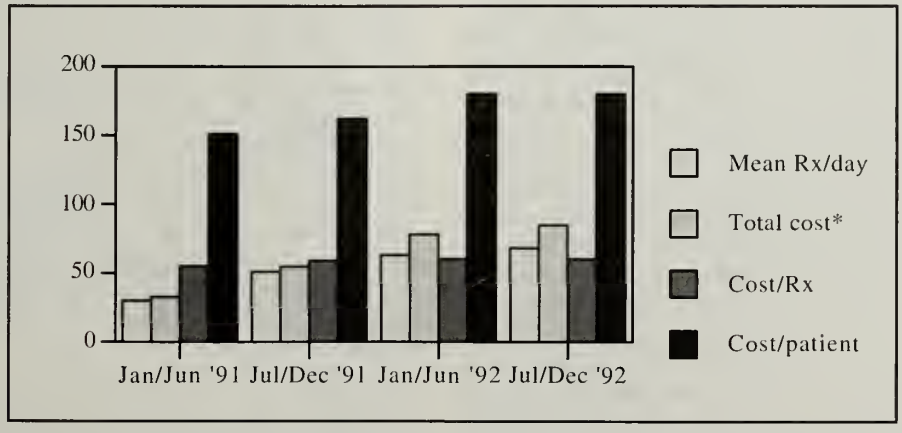

Figure 2.—The graph shows the Madison Clinic's AIDS workload, the mean number of drugs prescribed per day, and the total and mean costs of drug therapy. *Costs given in thousands (1993, unpublished data).

would be covered by employers when they were employed. These are imperfect data; respondents have been selected for the advanced state of their illness or for their poverty, which confounds any analysis of employment status. Even this severely limited information suggests that most persons with HIV infection or AIDS may be unemployed and thus protected later by insurance coverage schemes reliant on employer implementation.

Where Will Persons With HIV Infection Receive Care?

The Washington State legislation calls for a statewide plan for health personnel and resources that would guarantee physical access to primary health care. The state has a shortage of medical practitioners in many areas, and the intent is to ensure that the move to managed care and universal health insurance does not come at the expense of accessibility of medical care.

Since 1988 the Department of Health has financed and administered the HIV Intervention Program, which recruits physicians to care for persons with HIV disease. These practitioners are then assured of reimbursement by the state on a fee-for-service basis. Recruitment patterns were analyzed to discover the relationship between recruitment and the residence of persons with HIV disease and to describe the relationship between practitioner shortage and recruitment into the HIV Intervention Program. A preliminary estimate of statewide coverage shows that recruitment has been successful: 26 of 39 counties now have HIV Intervention Program providers enrolled. Only 30 cases (less than 1% of class IV non-AIDS or AIDS) have been reported outside of these counties.

Enrollment of HIV Intervention Program providers is inversely correlated with the designation of a county as a medically underserved area (χ^2 8.6, $P < .005$, Table 2). This indicates that recruitment was more successful where there was an adequate number of health care professionals and that their distribution across the state is important to primary care for HIV disease, as it is for other diseases.

The Washington State legislation defines criteria for the inclusion of services for public financing that "shall include those health services that are effective and necessary on a societal basis for the maintenance of the health of citizens of the state, weighed against the need to control state services expenditures . . ." (Health Services Act of 1993, §449). Final decisions about including particular services will be decided by a five-member health commission appointed by the governor.

Pharmaceuticals will certainly be a topic for this commission's attention, although care for persons with HIV infection includes more than drugs. Long-term care, recovery from substance abuse, case management, and social support services are all part of primary care for this group. Drugs are an important benefit, however, and serve as a good example of the type of benefits required by persons with HIV infection.

The Washington State Department of Health and the Seattle-King County, Everett Ryan White Title 1 Consortium jointly administer the AIDS Prescription Drug Program to support the purchase of pharmaceuticals by persons with HIV infection or AIDS. This program covers the cost of purchasing 33 different medications such as antiretrovirals, antifungals, and antibiotics and has more than 700 persons enrolled.

TABLE 1.—*Employment Status and Income Level of Persons in Washington State With Human Immunodeficiency Virus Infection or Acquired Immunodeficiency Syndrome (HIV/AIDS), 1993, by Study*

	Employed, No. (%)		
SHAS Interviews*	*Full-time*	*Part-time*	*Unemployed*
(n = 200 men)	67 (34)	29 (15)	105 (53)
(n = 27 women).....	9 (33)	5 (19)	13 (48)
	Income Level, No. (%)		
HIP/APDP Database†	*No Income*	*<100% Poverty Level*	*100%-200% Paverty Level*
(n = 1,597)	449 (28)	258 (16.2)	526 (32.9)
	Insurance Status, No. (%)		
Insurance Cantinuation	*COBRA*	*High Risk*	*Other*
(n = 311).....	186 (60)	65 (21)	- - (19)

CO8RA = Consolidated Omnibus Budget Reconciliation Act

*The Supplement to HIV/AIDS Surveillance (SHAS) project conducts in-depth interviews of persons with AIDS. To date, 227 such interviews have been carried out, and only 34% of men and 33% of women were fully employed at the time they were interviewed.

†The combined HIV Intervention Program and AIDS Prescription Drug Program (HIP/APDP) serves persons with incomes 200% below the poverty level. Data suggest that at least 44% of recipients are not fully employed and earn less than the poverty level of $568 a month; full employment at the minimum wage guarantees an income of $680 per month.

Statewide data on benefits paid out are not yet available. Data from a large AIDS clinic in Seattle-King County was examined, however. As prescriptions are written, information on patients—patient number, prescription, dose, price, and total cost—are entered by the pharmacy staff. Information is compiled biannually to track performance, workload, and cost.

Costs recorded for prescription drugs have risen consistently since 1991 when records were first kept (Figure 3). The mean number of prescriptions filled per day increased from 36 scripts per day in late 1991 to 68 scripts in 1993. This increase was proportionate to the mean number of patients being seen each month—which increased from 200 to 411 over the same time span. The increase in the number of scripts per day is consistent with the increase in the number of persons using pharmacy services. The mean cost of prescriptions per patient also increased during this time from $163.50 per month in late 1991 to $218.30 per patient in early 1993. The average number of prescriptions per patient remained the same throughout this period, so this increase reflected an increased cost per prescription due to either an increase in the cost of the medicines prescribed or a tendency to prescribe greater amounts in each prescription.

Discussion

States are often laboratories for reform.[4,5] Our analysis suggests that information currently available at the state level is insufficient to ensure adequate care for persons with HIV infection and AIDS, if the implementa-

TABLE 2.—*Inverse Correlation of the Presence of a Provider in the Human Immunodeficiency Virus (HIV) Intervention Program (HIP) With the County Designation as a Medically Underserved Area (MUA) or Health Professional Shortage Area, Washington State, 1993*

HIV Intervention Program	County, No.		
MUA or HPSA	Yes	No	Total
HIP provider recruited in county	4	22	26
HIP provider not recruited in county	8	5	13
Total	12	27	39

tion of health care reform includes incorporating existing categoric programs for AIDS into new care delivery schemes. In public health planning, decision makers will need more information on the current delivery of prevention services, including estimates of population coverage, the number of persons referred to primary care from public counseling, testing, and case management services, and the completeness of partner notification. Although much of this information could be gleaned from existing sources such as the studies of knowledge, attitude, and practice done by the Department of Health and intake data of the HIV Intervention Program and AIDS Prescription Drug Program, some investment of personnel and computer time would be necessary.

The oversight of employer-based insurance and a basic health plan should include monitoring enrollment to ensure that persons infected with HIV are included in a timely way. The persistence of clauses excluding preexisting conditions and the creation of heavy copayments for antiretroviral drugs suggest that a basic health plan will not serve the needs of this group. Until financial access can be ensured, existing programs such as insurance continuation must be retained. In the short term, it is not safe to rely on employer-based coverage alone for persons with HIV infection or AIDS because unemployment is high in this group compared with a statewide figure of 11.3% unemployed (Office of Financial Management, "1990 Washington Health Care Estimates: A Resource Publication for Policy Analysts," 1991). In Washington State, employment-based schemes will not cover those currently ill until 1999. This is consistent with national studies of employment status among persons with HIV infection or AIDS and the role of employer-based insurance in financing health care for this group.[6,7]

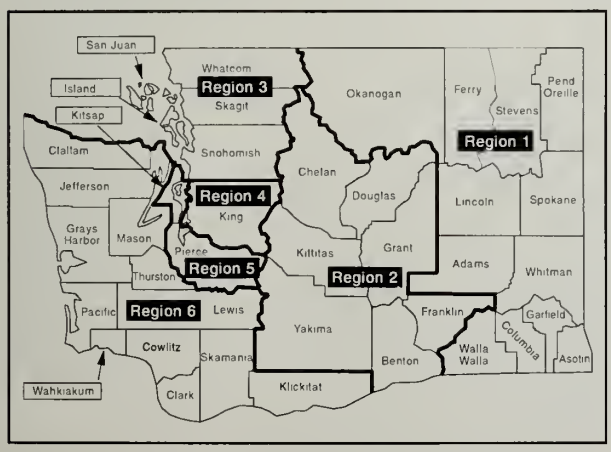

Figure 3.—The map shows the AIDSNETS [AIDS Service Network System] regions of Washington State.

To reinforce access, planning for health personnel distribution should include data on where people with HIV infection or AIDS currently receive care. Studies have described possible limitations of the managed competition approach in rural areas where shortages exist.[8] Our review indicates that constraints on the availability of health care professionals also affect the capacity to recruit persons into categoric access programs of primary care of HIV disease. To ensure geographic access to care, tracking of HIV providers among plans is recommended.

Geographic access is only one among many possible barriers to care recognized in the Washington State legislation. Additional ones include the training of providers[9] and attitudes of health care professionals towards this stigmatized illness[10]—barriers that need to be overcome if AIDS care is to be successfully incorporated into a basic benefits package.

Clinic-based information currently available is adequate to estimate costs of therapies and prescribing practices. In view of new prophylactic therapies for infections with *Mycobacterium avium*, *Pneumocystis carinii*, and other opportunistic pathogens, it is not surprising that costs are rising and likely will continue to rise. Despite the expense of drug regimens, savings are being realized in the care of HIV infection because such regimens reduce the length of hospital stays.[11] Such information on a state-by-state basis could inform decisions about benefits by such groups as the Washington State Health Commission.

Determining what should be included in the basic benefits package will be important to persons infected with HIV. Our initial attempt to quantify the current costs and patterns for pharmaceutical use in this group was hindered by the lack of data. Deliberations on public financing for this care will require information on the cost-effectiveness of these regimens and documentation of their use as an alternative to hospital stays. Studies to date suggest that such information is obtainable.[12,13]

Health care for persons with HIV infection or AIDS represented only 2% of the health care dollars spent in Washington State in 1991.[14] The importance of HIV infection is less an issue of fiscal impact and more an issue of integrating communicable disease control and the care of patients with a terminal disease into health care reform.

During any reform of the health care system, the ability to assure epidemic disease control and the compassionate societal response to chronic debilitating diseases must be safeguarded. Both of these elements are central considerations in dealing with the ongoing HIV epidemic and in caring for those affected. Thus, defining

the effects of reform on this population serves as a paradigm for considering broad issues in public health and health services.

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* * *

AT LAST

Morphine drips like sapphire,
deep fire, heat.
She sighs, but her trachea
gurgles like Mimi's
never did. So much
for romance, opera,
with her body cold
beyond the knees and elbows.
She watches the priest,
a nice man, holding a hand,
hers. She can't feel it.
So much for deathbed solace
promised by the Church.
"I bless the medicine
that takes the pain away,"
she murmurs, giving him
something more substantial
to hold on to. His gasp's
a soft ooh, *belle canto*.

"Heaven," he's saying, "jewel
in Mary's crown," but that's not where
she's heading when she gives up
the ghost. She's aimed for limbo.
Not a place she ought to want
to go, they've told her,
and told her. Baloney.
That's where her lilac-blue
baby waits. She's bringing
knees to dandle her on, arms
to hold her, a drowned-lung lullaby
to croon her fast asleep
at last. Forever, her mother.

J. C. Todd©
Philadelphia, Pennsylvania

Conferences and Reviews

Screening for Prostate Cancer

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Prostate cancer is a serious health care problem in the United States. Whether or not to screen for it has become a timely issue. Although a large number of men have clinically important, asymptomatic, undetected prostate cancer, an even larger number have clinically unimportant cancer. To justify screening programs, not only must we avoid detecting biologically unimportant cancers, we must also detect and effectively treat that subset of tumors that, if undiagnosed, would progress, produce symptoms, and reduce life expectancy. Serum prostate-specific antigen (PSA) assay, or its variations such as PSA density, PSA velocity, and age-specific reference ranges, and the digital rectal examination are the best tests for detecting clinically important, asymptomatic, curable tumors. Recent data suggest that using serum PSA levels does not result in an overdetection of unimportant tumors. Highly effective, curative treatment of localized prostate cancer is available. These factors promote optimism that screening for prostate cancer will ultimately prove beneficial. Nonetheless, men should be informed regarding the benefits and possible risks before being screened for prostate cancer.

(Cher ML, Carroll PR: Screening for prostate cancer. West J Med 1995; 162:235-242)

Prostate cancer is increasing in importance as a health care problem in the United States. The incidence has risen steadily over the past 25 years, with a projected 200,000 new cases in 1994.[1] Prostate cancer has now surpassed lung cancer to become the most common clinically detected non-skin tumor in men. This rising incidence is due to a combination of factors including aging of the population, increased detection efforts, and technologic advances resulting in improved detection of early-stage tumors. In fact, the percentage of patients with localized disease at the time of diagnosis has risen from 57% in 1974 to 64% in 1990.[2]

The perception of prostate cancer as an indolent disease with little clinical impact is incorrect. In fact, prostate and breast cancers have similar epidemiologic characteristics: for men and women, each is the second leading cause of cancer death in the United States, accounting for a projected 38,000 and 46,000 deaths, respectively, this year. The proportion of breast and prostate cancers localized at the time of diagnosis is similar; the higher mortality of lung cancer is due to an increased proportion of disseminated cases at diagnosis. Prostate cancer has its highest mortality at age 75 and older; breast cancer affects women across many age groups, with the highest mortality occurring between ages 55 and 74 years.[1]

Prostate cancer is seldom found in men younger than 50.[3] Although its incidence is higher in African Americans, most tumors are found in whites.[3,4] Men with a family history are at an increased risk: those with one or two first- or second-degree relatives (maternal or paternal) with prostate cancer have an age-adjusted relative risk 2 to 11 times greater than that of the general population.[5-7]

Increased public awareness of prostate cancer has led to considerable debate over detection and management issues. Whether or not to screen for prostate cancer has become a topic of current debate. Intuition suggests that if a screening program detects localized tumors in asymptomatic men, survival rates will improve. The recognized ability of surgical therapy and irradiation to cure organ-confined prostate cancer and the proven benefit of screening programs for breast cancer support this notion.[8-10] Other unproven possible benefits include reduced disease-specific morbidity and a continued productive lifestyle. These potential benefits must be weighed against the risks of screening. As yet, however, no consensus has been reached. Screening with serum PSA levels has been endorsed by the American Urological Association, the American College of Radiology, and the American Cancer Society, but not by the National Cancer Institute or the Canadian Task Force on the Periodic Health Examination. In this article we highlight areas of controversy and present current information on test performance and the economic effect of screening.*

Prostate Cancer—A Spectrum of Disease

Autopsy studies show a high prevalence of histologically recognizable cancers in men with no clinical manifestation of disease[11,12]—about 30% of men older than 50. Most of these cancers are small, confined, of low prolif-

*See also the editorial by J. N. Kabalin, MD, "Screening for Prostate Cancer Today," on pages 272-273 of this issue.

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ABBREVIATIONS USED IN TEXT

DRE = digital rectal examination
PSA = prostate-specific antigen
TRUS = transrectal ultrasonography

erative rate,[13] and pose limited risk to the men in whom they are found. Prostate cancer screening programs must avoid detecting these clinically unimportant tumors. If they are detected, many men would suffer needlessly from the morbidity and mortality of treatment—impotence, incontinence, treatment-related death—as well as from the psychological effects of knowing that they have cancer. Even low-volume cancers, however, can progress and have notable clinical effects, especially in young healthy men likely to live a long time.

Clinically important prostate cancers can be defined as those that threaten the well-being of a man within his remaining life expectancy. Epidemiologic data have been used to estimate the proportion of prostate cancers that are clinically important.[14] Autopsy studies have shown that the risk that histologic (autopsy- or clinically apparent) prostate cancer will develop in a 50-year-old man in his lifetime is 42%. The lifetime risk of clinically apparent disease developing in a 50-year-old man is 9.5%.[15] Therefore, approximately 9.5 per 42, or 23%, of cases of cancer are clinically important.

Pathologic data lead to a similar estimate. Although perfect markers of progression have not been established, pathologic variables such as volume, grade, and pattern of growth have been linked strongly to biologic behavior. These characteristics have been evaluated in occult prostate cancers discovered at autopsy after death from unrelated reasons and in cystoprostatectomy specimens in patients with bladder cancer. These studies likewise lead to the conclusion that about 20% of cases of currently undetected cancers are clinically important.[14] As 30% of men older than 50 have histologic prostate cancer,[11] we can calculate that about 6%—20% of 30%—of men have clinically important prostate cancer. Therefore, a large pool of men with clinically important but undetected prostate cancer exists, and the rationale for screening rests on detecting these cancers.

Although these epidemiologic and pathologic considerations appear to provide a rational basis for prostate cancer screening programs, a randomized clinical trial would allow a more definitive evaluation of the cost-benefit ratio. A screening trial must randomly allocate men to screened and unscreened groups to eliminate lead- and length-time bias. Lead-time bias can result in artificially prolonged survival in an uncontrolled, screened group—even if the treatment applied has no effect on the natural history of the disease—due to the measurement of survival from the time of detection rather than from the time of the development of symptoms. Length-time bias is based on the premise that men who present for screening programs harbor a disproportionate number of slowly growing tumors.

A successful screening program must not only avoid detecting biologically unimportant cancers, but it must also detect those asymptomatic tumors that, if undiagnosed, would progress, produce symptoms, and reduce life expectancy. Thus, we must understand the biologic and epidemiologic characteristics of clinically important tumors and then determine if the tumors detected by currently available screening tests have similar characteristics.

Current Screening Tests

The digital rectal examination (DRE), transrectal ultrasonography, and serum PSA tests are used for detecting prostate cancer. Table 1 outlines the frequency of an abnormal ("positive") result and the cancer detection rate for these tests.[4,16-33] Evaluation of a screening test involves determining its sensitivity and specificity. To determine the true-positive, true-negative, false-positive, and false-negative rates of a given test, the underlying prevalence of the disease—the denominator in these rates—must be known. Care must be taken when reading the literature to assess how disease prevalence was determined. Because most studies do not take into account the underlying (autopsy) prevalence,[34] current literature reports probably overestimate the tests' sensitivity and specificity in detecting disease in asymptomatic screening groups. This discrepancy in test performance is outlined in Tables 2 and 3.[34] Given that the goal of screening should not be to detect clinically unimportant tumors, however, test performance as reported may be appropriate.

The factors that motivate doing a biopsy in any given study (increasing the biopsy rate increases the number of cancers diagnosed) should also be examined.[35,36] For these reasons, each study is best interpreted as determining the relative value of the various screening techniques with respect to each other, rather than the absolute sensitivity and specificity of individual tests.

Digital Rectal Examination

Several studies have addressed the ability of the DRE to detect prostate cancer in asymptomatic patients.[4,16-22] Abnormalities were found in 3.2% to 10% of screened men, leading to biopsy findings of cancer in 0.2% to 1.7%

TABLE 1.—*Performance Characteristics of Screening Tests*

Test	*Positive Result, % of Tests*	*Concer Detection Rote, % of Populotion*
Digital rectal examination*	3.2-10	0.2-1.7
Transrectal ultrasonogram†	7.0-60	2.0-20
Prostate-specific antigen, >4.0 ng/ml‡§	9.0-15	2.5-3.0
Prostate-specific antigen, >10.0 ng/ml	2.0-0.3	1.0-1.5

*From Thompson et al[4]; Gilbertsen[18]; Chodak and Schoenberg[17]; Vihko et al[16]; Imai et al[19]; Lee et al[20]; Waaler et al[21]; Chodak et al.[22]

†From Lee et al[20]; Cooner et al[23,24]; Devonec et al[25]; Fritzsche et al[26]; Gustafson et al[27]; Perrin et al[28]; Lee et al[29]; Nesbitt et al.[30]

‡From Catalona et al[31]; Catalona et al[32]; Brawer et al.[33]

§Normal, <4.0 ng/ml.

TABLE 2.—*Performance Characteristics of Screening Tests Based on Biopsy Findings of Cancer ('Positive')*

Test	Sensitivity, %	Specificity, %	Positive Predictive Value, %
Digital rectal examination...	45-58	96-97	24-58
Transrectal ultrasonogram...	71-91	89-94	15-43
Prostate-specific antigen, > 4.0 ng/ml*	67-89	59-97	33-47

*Normal, <4.0 ng/ml.

of the original group. An interpretation of these percentages is that the DRE detects a relatively low percentage of men with early-stage carcinoma of the prostate. These numbers reflect the inherent subjectivity of this examination, which depends in part on a physician's index of suspicion as well as the epidemiologic and symptomatic aspects of a patient's presentation. On the other hand, for a patient in a physician's office for any reason, the DRE is inexpensive, relatively noninvasive, and has potential benefits unrelated to prostatic disease. The American Cancer Society recommends a yearly DRE and fecal occult blood test for all men older than 40 years.

Transrectal Ultrasonography

Transrectal ultrasonography is a relatively invasive and expensive study not immediately or widely available to all primary care physicians. In addition, this technology suffers from a lack of specific findings.[37] Several studies have shown that prostate cancer can produce hypoechoic, isoechoic, and hyperechoic patterns.[38] The predominant appearance is hypoechoic,[39,40] however, and improved diagnosis rates per biopsy have been obtained by concentrating only on peripheral hypoechoic lesions.[30] Although this approach may increase the percentage of biopsies that reveal cancer, it will likely increase the number of cancers that go undetected. Transrectal ultrasonographic findings have been interpreted as abnormal in 7% to 60% of studies, resulting in the identification of tumors in 2% to 20% of the original group screened.[20,23-30] The wide discrepancy in these percentages results from the different indications for biopsy and the presence or absence of urologic symptoms in the study groups. Overall, they suggest that if TRUS were used as an initial screening tool, a higher number of patients would be diagnosed with cancer than would be with DRE alone; but the specificity falls relative to DRE in that more patients would be subjected to a biopsy with normal findings (negative). It should be noted that most of these studies are not true screening programs and may contain a higher percentage of patients with urologic symptoms than would be found in a truly screened population, resulting in an overestimation of the value of TRUS.

TABLE 3.—*Performance Characteristics of Screening Tests Based on Underlying Autopsy Prevalence of Disease ('Positive')**

Test	Sensitivity, %	Specificity, %	Positive Predictive Value, %
Digital rectal examination...	3.7	92.0	18.5
Transrectal ultrasonogram...	22.4	72.6	3.8
Prostate-specific antigen, >4.0 ng/ml†.....	28.5	73.7	34.4
Prostate-specific antigen, >10.0 ng/ml.....	13.5	91.0	55.0

*From Optenberg and Thompson.[34]
†Normal, <4.0 ng/ml.

The pathologic characteristics of tumors detected by transrectal ultrasonography have been examined in several series.[20,40-42] The stage and volume appear similar to those detected by DRE. The limitation of TRUS is not that too many tiny, unimportant cancers are diagnosed, but rather its cost, invasiveness, and limited advantage in addition to DRE and PSA in sensitivity. For these reasons, few investigators have recommended it as the initial tool in screening protocols.

The development of the spring-loaded biopsy gun has made it easy to obtain multiple tissue cores from the prostate without anesthesia. The biopsy gun can be used in conjunction with TRUS to obtain systematic, spatially separated quadrant or sextant biopsies throughout the gland (regardless of the echo pattern) after other factors determine that a biopsy is warranted. If hypoechoic lesions are seen, they may be biopsied as well. Although TRUS has an important role in the management of patients with known prostate cancer, to detect asymptomatic prostate cancer, it should be used only as a tool to assist in biopsy.

Prostate-Specific Antigen

Prostate-specific antigen is a serine protease produced by normal, hyperplastic, and malignant prostatic epithelium. Its serum level correlates with benign and malignant prostatic volume. Four PSA assays are currently available, but none are approved by the Food and Drug Administration for prostate cancer screening. The serum PSA has proved to be a powerful tumor marker in urologic patients, and previously the assay was used most often to monitor response to treatment: an undetectable serum PSA level after the prostate is removed indicates no evidence of disease[43]; a rising PSA level, whether after radiation therapy, radical prostatectomy, or systemic therapy, usually predicts disease progression months to years before it becomes apparent clinically.

Several problems occur with using serum PSA measurements as a screening tool for the early detection of asymptomatic prostate cancer. Patients with benign prostatic hyperplasia—or any other prostatic disease—may have an elevated value, and about 15% to 20% of patients with localized, asymptomatic prostate cancer will not.[44,45] If primary care physicians decide to use serum PSA assays to screen asymptomatic patients, they must define a threshold value for referral to a urologist. Likewise, a urologist must define a threshold value for TRUS or biopsy. A lower threshold will result in more cancers detected, but will also lead to a higher number of unnecessary biopsies. The best threshold level is still unknown.

Although many series in the literature use serum PSA assays as part of a multiple test screening protocol, few use elevated serum PSA levels as the sole criterion for biopsy. Only a few studies use the serum PSA measurement as the initial screening tool, and these are most analogous to the situation of a primary care physician ordering a serum PSA test on patients with no prostatic symptoms.

It is important to note that these studies have different indications for biopsy. One group found that threshold levels of 4.0 and 10.0 ng per ml resulted in 9.4% and 2% of men, respectively, having positive test results.[31] The subsequent respective cancer detection rates of 34% and 59% of those with a positive PSA assay represented 3% and 1.3%, respectively, of the original population. The protocol used required biopsy only in those men with abnormal findings on either DRE or TRUS; the biopsy rate was 95% for those with an elevated serum PSA level, however. In another large-scale, multicenter study with a liberal biopsy policy, 15% of men had a serum PSA level of greater than 4.0 ng per ml, and 4.4% of those undergoing biopsy had cancer—2.9% of the original group.[32] In a similar study, a positive test rate of 15% and 3% for the thresholds of 4.0 and 10.0 ng per ml, respectively, was reported, and the respective cancer detection rate was 30% and 50% of the men who underwent biopsy—2.5% and 0.7%, respectively, of the original group.[33] The biopsy policy in this study was also liberal in that these investigators attempted systematic sextant biopsies on every man with a serum PSA level of greater than 4.0 ng per ml; unfortunately, only 56% of such patients agreed to undergo ultrasonography and biopsy. Correcting for those who refused biopsy, the cancer detection rate for the original population would be approximately 4.5% and 1.5%, respectively, for the two threshold levels.

Urologists do not agree on the indications for biopsy and whether or not to do systematic quadrant or sextant biopsies. For example, a serum PSA level above an arbitrarily set threshold will prompt some urologists to do systematic TRUS-guided biopsies even if the DRE and TRUS images are interpreted as normal. Other urologists will do a biopsy only if a hypoechoic lesion is seen on TRUS or if there is a palpable induration or nodule.

Recent clinical research has led to possible improvements in the methods of using serum PSA values. These methods, PSA density, PSA velocity, and age-specific reference ranges, may allow increased sensitivity and specificity in detecting clinically important tumors. Each of these techniques represents an attempt to separate the contributions of prostate cancer and other prostatic diseases (mostly benign prostatic hyperplasia) to the serum PSA level.

Prostate-specific antigen density, or index, is the serum PSA value divided by the volume of the prostate.[46] This calculation is made in an attempt to factor out the contribution of benign prostatic hyperplasia to the serum PSA value. Its usefulness is currently a matter of debate.[47,48] It may be superior to the PSA assay alone in determining the need for systematic biopsy in patients with an elevated serum PSA level but normal findings on DRE and TRUS. Biopsy may be avoided in those with a low PSA density who do not have hypoechoic lesions. The test characteristics of both PSA and PSA density used for screening in patients with elevated serum PSA levels and normal findings on DRE and TRUS are noted in Table 4.[49] An obvious drawback of PSA density in screening programs is the need to use TRUS to determine the prostate volume.

TABLE 4.—*Use of Prostate-Specific Antigen (PSA) and PSA Density to Detect Prostate Cancer in Men With Normal Digital Rectal Examination (DRE) and Transrectal Ultrasonogram (TRUS) ('Negative')**

Threshold	*Sensitivity, %*	*Specificity, %*	*Positive Predictive Value, %*
PSA, ng/ml			
4.0	95	13	27
6.0	92	28	30
12.0	55	71	39
20.0	24	86	39
PSA density			
0.10	95	24	29
0.15	79	50	34
0.30	45	85	50
0.50	29	95	65

*From Shinohara et al.[49]

Prostate-specific antigen velocity refers to the rate of change of serum PSA levels.[50] Retrospective study has shown that men with prostate cancer have a more rapidly rising serum PSA level in the years before diagnosis than men without prostate cancer. Men whose serum PSA value increases by 0.75 ng per ml a year appear to be at increased risk. In one study, the sensitivity and specificity of the PSA velocity were 72% and 90%, respectively—elevated PSA levels alone had a sensitivity of 78% and specificity of 60%.[50] The PSA velocity must be interpreted with caution, however. An elevated PSA velocity should be considered important only when several serum PSA assays are carried out by the same laboratory over at least 18 months.

Not surprisingly, the serum PSA level (and prostatic volume) in men without prostate cancer is moderately correlated with age.[51,52] Age-specific reference ranges have been developed that can be used to determine the upper limits of normal (Table 5).[52] Decreasing the normal level in younger patients and increasing it in older patients would increase the sensitivity of the test in the former group and the specificity in the latter. Fewer older patients, in whom diseases other than cancer contribute relatively more to the serum PSA level, would have false-positive tests. The usefulness of these concepts—PSA density, PSA velocity, and age-specific PSA level—is being tested in clinical trials.

A final refinement of the use of the PSA assay is the differentiation between bound and unbound forms. Preliminary data suggest that the free, noncomplexed form of serum PSA constitutes a smaller proportion of the total

TABLE 5.—*Age-Specific Prostate-Specific Antigen Reference Range**

Age, yr	*Reference Range, ng/ml†*
40-49	0.0-2.5
50-59	0.0-3.5
60-69	0.0-4.5
70-79	0.0-6.5

*From Oesterling et al.[52]
†Based on the current normal assay range of 0.0 to 4.0 ng/ml.

PSA level in prostate cancer than in benign prostatic hyperplasia.[53]

Screening Tests Compared

Several investigators have examined the yield of PSA tests, DRE, and TRUS in various patient groups. Cancer detection rates and the number of TRUS-generated biopsies necessary to detect cancer for various combinations of tests are summarized in Table 6.[54] The patient group studied, initial screening method—PSA assay alone or a combination of tests—and the indications for biopsy varied considerably among studies. The results in Table 6 support using the PSA measurement and DRE as initial screening tests; the use of TRUS should be reserved for biopsy and staging. The addition of serum PSA testing to the DRE adds substantially to detection rates. In screening trials that use both the DRE and PSA assay, the positive predictive value for the serum PSA level is 32% to 43% and for DRE, 21% to 24%.[39,41,55,56] The performance characteristics of DRE and PSA test, alone and in combination, from the American Cancer Society Prostate Cancer Screening Project are summarized in Table 7.[39,41,55]

Screening tests should also be evaluated for their sensitivity and specificity in detecting clinically localized, and therefore possibly curable, cancers. Pathologic staging has shown that many clinically localized tumors detected by DRE are not confined to the prostate gland. In one series of palpable tumors—clinical stage B or T1-2—63% extended through the capsule and 18% into the seminal vesicles. The mean volume was 4.04 cc.[57] These tumors are on average about ten times larger than minimal tumors detected by transurethral resection done for

TABLE 6.—*Performance of Screening Tests in Combination**

Test Results				
DRE	*PSA*	*TRUS*	*TRUS/Biopsy: Cancer*	*Detection Rates, %*
+	+	+	1.8:1	56
−	+	−	3.4:1	29
−	+	+	3.7:1	27
+	+	−	4.0:1	25
+	−	+	6.2:1	16
+	−	−	12.5:1	8
−	−	+	14.0:1	7
−	−	−	--	0

DRE = digital rectal examination, PSA = prostate-specific antigen, TRUS = transrectal ultrasonogram, + = positive (or abnormal findings), − = negative (or normal findings)

*Modified from Brawer.[54]

TABLE 7.—*Performance of Digital Rectal Examination (DRE) and Prostate-Specific Antigen (PSA) Assay Alone or in Combination**

Performance	*PSA > 4 ng/ml*	*Abnormal DRE*	*Abnormal DRE or PSA > 4 ng/ml*	*Abnormal DRE and PSA > 4 ng/ml*
Sensitivity, %	67	50	84	34
Specificity, %	97	94	92	99.5
Positive predictive value, %	43	24	28	49

*As calculated from the American Cancer Society Prostate Cancer Screening Project.[39,41,55]

presumed benign disease (stage T1a)[58] and about 50 to 100 times larger than those found incidentally in cystoprostatectomy specimens.[59] Thus, DRE detects relatively late cancers of large volume that are most often not confined to the prostate. Also, as DRE findings do not correlate well with tumor volume,[60,61] it occasionally uncovers tiny unimportant tumors located near the rectal surface. For these reasons, DRE alone is not a sensitive and specific tool for detecting clinically important, curable tumors.

Most serum PSA-detected tumors are potentially curable. In one PSA-driven screening program, 29% to 37% of patients with PSA-detected cancers had advanced disease compared with 57% of patients in the nonscreened comparison group.[31] Data are also accumulating that only a few PSA-detected tumors are clinically unimportant. In the above series, the number of potentially unimportant (well-differentiated and microscopically focal) cancers detected by the serum PSA assay (3% to 8%) was not significantly different from that detected in the nonscreened group (3%). Another study found that nonpalpable cancers detected by serum PSA testing had clinical and pathologic characteristics similar to those of palpable cancers. Few tumors were considered unimportant on the basis of volume, and more than 80% were found to be early-stage cancers.[62] Other reports corroborate these findings. A group of men with nonpalpable prostate cancer (stage T1c), most of whom were referred for biopsy because of an elevated serum PSA level, was compared with a group of men with palpable disease (stage T2) and another group with minimal disease detected by transurethral resection done for presumed benign prostatic hyperplasia (stage T1a).[58] Detailed pathologic analysis of the radical prostatectomy specimens showed that the group of men with impalpable tumors had tumors of stage, grade, and volume intermediate between the other two groups. The investigators thought that 16% were unimportant compared with 2% of the palpable and 33% of the stage T1a tumors.[58] They further assessed for preoperative measures that could assist in differentiating between men with important and those with unimportant disease. Transrectal ultrasonographic findings were not helpful. An elevated serum PSA level differentiated most patients with important disease, although its use alone had a low negative predictive value—too many patients with a low serum PSA level had significant disease. The model that provided the highest positive and negative predictive

values for substantial disease involved a combination of PSA density and the volume and the grade of tumor on multiple biopsy cores. With this model, most of the radical prostatectomies done on patients with unimportant disease could have been avoided.

Not only is the serum PSA assay more sensitive than DRE, it is much more closely linked to tumor volume and pathologic staging results. Serum PSA values or variations such as PSA density are promising screening tools because they seem to increase the detection of clinically important cancers without substantially increasing the detection of clinically unimportant tumors.

Net Benefit of Screening

Total costs in the United States have been estimated for various screening scenarios for prostate cancer. One calculation is that there are 23.8 million men in the United States aged 50 to 74 years.[55] Because 11% have substantial cardiovascular disease, approximately 21.2 million men remain as possible candidates for screening. If both the PSA assay and DRE are used and TRUS-directed biopsy is reserved for those with positive findings, the cancer detection rates would range from 1.1% to 5.5% for various age groups. About 650,000 men would be found to have cancer (compared with 200,000 men expected to be diagnosed in 1994). Of these men, 95% will have localized disease. If two thirds receive radical prostatectomy and a third receive radiation therapy—mortality rates estimated at 1.2% and 0.5%, respectively—2,000 to 6,000 extra deaths will occur from screening.[55] Using different assumptions, others estimated that approximately 26,000 excess deaths would occur during the first year.[34] For a net mortality benefit, screening would have to avert more than these numbers of deaths in the ensuing years, and this may be reasonable considering that the ten-year cause-specific survival rate of men with untreated prostate cancer is 34% to 87%, depending on the grade.[63]

Using these assumptions, investigators calculated the cost of the first year of a screening program to be about $5 to $14 billion,[55] and others estimated it at $28 billion.[16] Of course, these costs would be reduced over the long term by saving money spent on treating advanced disease and by limiting serial screening to two or three years because the diagnosis rate falls and the population would be depleted of men with detectable prostate cancer.

Another method of considering the economic aspects of screening is estimating marginal costs of various screening scenarios and then doing a benefit-cost analysis by converting various perceived benefits and costs of staging and treatment into dollar values.[64] In three years of the American Cancer Society's National Prostate Cancer Detection Project, 1,449 men were screened (serial screening). Marginal costs (cost per case of cancer diagnosed) for screening based on any test increased substantially during the second and third year of the screening trial because fewer cases of cancer were detected in the second and third years. During the first year, DRE was less expensive than the PSA-based screening scenarios; however, because of its limited sensitivity, by the third year the average costs per case of cancer diagnosed were similar between DRE ($3,415) and any of the PSA-based scenarios ($4,482 to $6,594). True cost-efficacy calculations could not be done as there are no data demonstrating a reduction in mortality from prostate cancer screening. A benefit-cost analysis was done, however, that gave the net cost in dollars per man for various screening scenarios. These results take into account factors such as morbidity of treatment and should be considered in terms of dollar costs, not overall benefit (Table 8).[62]

Two factors related to the serum PSA assay could greatly reduce the cost of PSA-based screening. First, if refinements in PSA testing could increase the specificity by a small amount (4%), the cost per case of cancer diagnosed would be less for PSA assays than for DRE done by a skilled examiner. A similar benefit would be achieved by reducing the cost of a PSA test below $30. These estimates show that the economic cost of PSA-based screening for prostate cancer is similar to the cost of screening for breast cancer with mammography.[64]

Although the costs of treating men with early prostate cancer are high, those for treating advanced disease are considerable as well: androgen deprivation therapy varies between $4,000 and $9,200 a year, chemotherapy between $3,600 and $5,380 a month, transurethral resection to manage outlet obstruction is about $9,160, and a single administration of strontium-89 chloride to manage bone pain is about $3,700. These values exclude costs associated with laboratory testing, imaging, pain control, visits to the office or emergency department, and hospital admissions not associated with the surgical procedures described earlier.

Treatment

For screening programs to be effective, curative treatments must be available. As discussed earlier, most tumors detected in PSA-driven screening programs are clinically important and potentially curable. The primary treatment options for clinically localized prostate cancer currently include radical prostatectomy, external beam or interstitial irradiation, cryotherapy, androgen withdrawal, and watchful waiting. Both radiation therapy and radical prostatectomy are regarded as potentially curative. The ten-year cause-specific survival of patients treated with radical prostatectomy is more than 90%.[65,66] Although such figures raise hopes that prostate cancer screening could result in reduced disease-specific mortality, the efficacy of active treatments over watchful waiting has been

TABLE 8.—*Benefit-Cost Analysis for Various Screening Scenarios**

Screening Test	*Cost/Case of Cancer Diagnosed, $*
DRE—skilled examiner	474
DRE—general detection effort	4,112
DRE + PSA, > 4.0 ng/ml	1,646
PSA, > 4.0 ng/ml	1,126

DRE = digital rectal examination, PSA = prostate-specific antigen

*Modified from Oesterling et al.[62]

questioned. Analysis of several series of patients managed initially with watchful waiting has shown that although prostate cancer is progressive, its natural history may be protracted.[63] A recent decision-analysis calculation—taking into account the morbidity of treatment—concluded that radical prostatectomy and radiation therapy had possible benefit over expectant management only for younger patients with higher-grade tumors.[67] In this study, however, the calculated benefit was exquisitely sensitive to the estimated prostate cancer progression rates, and thus the benefits of treatment were probably underestimated.

To Screen or Not to Screen?

The case for prostate cancer screening is supported by the following: the disease is burdensome in this country, serum PSA assays improve the detection of clinically important tumors without notably increasing the detection of unimportant tumors, most PSA-detected tumors are curable, and curative treatments are available. At this time, however, there are no data to confirm that screening reduces morbidity and mortality. Without these, the net benefit of screening cannot be calculated or predicted. Several studies are in progress. In the Prostate, Lung, Colon, Ovarian trial supported by the National Cancer Institute, men are randomly assigned to screening (with DRE and PSA assay) and to no screening, with cancer-specific mortality as the end point. The fact that therapy is not standardized and that screening will occur over only a limited time period may make the interpretation of results difficult, however. The efficacy of treatment is currently being examined in Scandinavia, where two randomized trials compare watchful waiting with radiation therapy or radical prostatectomy. A similar trial, Prostatectomy Versus Observation for Clinically Localized Carcinoma of the Prostate (PIVOT), has been proposed in the United States. Such trials, although imperfect, may give us the information we need for prostate cancer screening and treatment to be recommended with confidence.

In summary, many factors must be considered by both clinicians and their patients who are contemplating screening for prostate cancer. Standardized informed consent has been recommended before a screening test such as a serum PSA assay is ordered.[68] The information provided should attempt to answer such questions as the likelihood that an unscreened asymptomatic man will be adversely affected by prostate cancer in his lifetime, whether the screening test will lengthen or improve his quality of life, the chances of having a false-positive result and its consequences, the value of a normal result, and the recommendations of various experts. At our institution (UCSF), we recommend that relatively young, healthy, asymptomatic men obtain a serum PSA assay. We more strongly encourage screening in certain populations with a higher disease prevalence or mortality, such as African-American men or men with a family history of prostate cancer. If prostatic cancer is detected, patients are carefully counseled regarding the benefits and risks of all treatment options, including watchful waiting. At present the data suggest that, if screening is to be done, the combination of DRE and serum PSA assay is best.

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Total Hip Arthroplasty

Discussants
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Total hip arthroplasty, or surgical replacement of the hip joint with an artificial prosthesis, is a reconstructive procedure that has improved the management of those diseases of the hip joint that have responded poorly to conventional medical therapy. In this review we briefly summarize the evolution of total hip arthroplasty, the design and development of prosthetic hip components, and the current clinical indications for this procedure. The possible complications of total hip arthroplasty, its clinical performance over time, and future directions in hip replacement surgery are also discussed.

(Siopack JS, Jergesen HE: Total hip arthroplasty. West J Med 1995; 162:243-249)

Total hip arthroplasty is an orthopedic procedure that involves the surgical excision of the head and proximal neck of the femur and removal of the acetabular cartilage and subchondral bone. An artificial canal is created in the proximal medullary region of the femur, and a metal femoral prosthesis, composed of a stem and small-diameter head, is inserted into the femoral medullary canal. An acetabular component composed of a high-molecular-weight polyethylene articulating surface is inserted proximally into the enlarged acetabular space (Figures 1 and 2). To yield successful results, these total hip arthroplasty components must be fixed firmly to the bone, either with polymethylmethacrylate cement or, in more recent uncemented designs, by bony ingrowth into a porous coating on the implant, resulting in "biologic" fixation.

Total hip arthroplasty is currently one of the most widely performed procedures in orthopedic practice in the United States.* Since its introduction in this country in 1969, it has proved remarkably successful in eliminating pain and restoring function in hips severely involved with diseases such as osteoarthritis. It is estimated that about 170,000 total hip arthroplasties are performed each year in this country and that about 300,000 are done worldwide.[1] The first total hip replacement is thought to have been done in London by Phillip Wiles in 1938.[2] The procedure was further developed in the 1950s by pioneers such as McKee and Farrar.[3] This early work laid the groundwork for the innovative studies of Sir John Charnley who, in the late 1960s, approached the problem of artificial hip joint design by using the biomechanical principles of human hip joint function.[4,5] Repeated trials and experimentation with various materials and prosthetic designs culminated in the creation of the Charnley low-friction arthroplasty, a procedure still considered by many to be the current standard of total hip replacement. The noteworthy innovations of Charnley's arthroplasty included the combination of a small-diameter—22-mm—femoral head with a high-density polyethylene acetabular component to reduce friction and fixation of these prosthetic components to bone with polymethylmethacrylate cement.

Since Charnley's original prosthesis was introduced, several variants of the artificial hip joint have been developed; none have proved to be superior in the clinical setting, however. For example, despite the theoretical advantage of a larger-diameter femoral head, which some think permits more motion, generates less stress, and dislocates less readily, the longevity of the Charnley prosthesis appears to be enhanced by the smaller-diameter head, which reduces friction and the amount of wear debris produced and results in a lower incidence of acetabular loosening.[6]

Revision total hip arthroplasty is carried out in patients where there is failure of a previously implanted prosthesis. In such cases, all cement and prosthetic components are removed carefully to avoid penetrating or fracturing the bone. New components are then implanted and fixed with either a cemented or uncemented technique. Surgical indications for revision arthroplasty include loosening of the prosthetic components, wear-debris osteolysis, acute or chronic deep infection, mechanical failure of the prosthetic components, and chronic recurrent dislocation. Surgical revision is technically more difficult than the primary total hip arthroplasty procedure, both because there is less bone stock to work with and because the removal of adherent cement or prosthetic components may result in fracture or perfora-

*See also editorial by T. A. DeCoster, MD, and D. Rivero, MD, "Total Hip Arthroplasty—A Cure?" on page 274 of this issue.

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tion of the bone. With each successive total hip revision, the risk of infection and symptomatic loosening may increase substantially.[2] The number of these procedures is increasing steadily because many of the primary total hip arthroplasties done in the 1970s are beginning to fail. Improved operative techniques and specialized revision prosthetic components are being developed to decrease the morbidity associated with revision operations.

Indications and Goals

The most common condition for which total hip arthroplasty is done is severe osteoarthritis of the hip, accounting for 70% of cases. The primary indication for this procedure is severe pain and the limitation in activities of daily living that it causes. To warrant doing total hip replacement, pain must be refractory to conservative measures such as oral nonsteroidal anti-inflammatory medication, weight reduction, activity restriction, and the use of supports such as a cane. It is generally preferred that total hip arthroplasty be done in patients older than 60 years because at this age, the physical demands on the prosthesis tend to be fewer and the longevity of the operation approaches the life expectancy of the patient. Other conditions for which the procedure may be indicated and which predispose to the development of secondary osteoarthritis include developmental dysplasia of the hip, Paget's disease, trauma, and osteonecrosis of the femoral head. Patients with rheumatoid arthritis, other collagen diseases such as systemic lupus erythematosus, and ankylosing spondylitis may benefit as well. The large number of operations performed each year reflects the fact that more than 90% of appropriately selected patients achieve complete pain relief and notable improvement in function.[7]

Despite this level of success, total hip arthroplasty occasionally may be associated with complications.

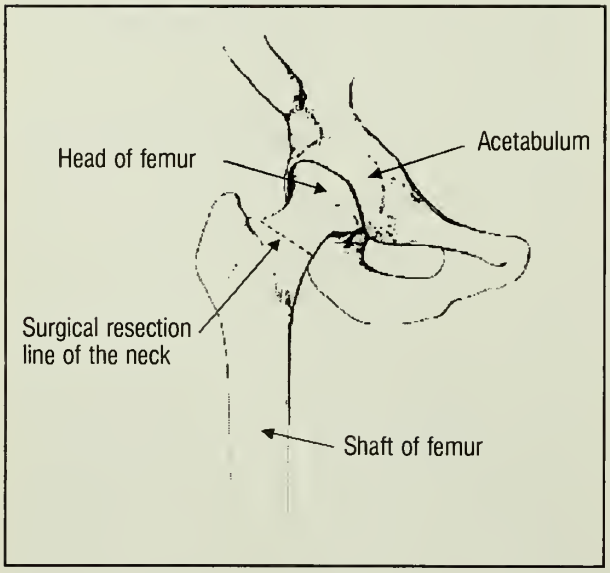

Figure 1.—Anatomy of a right hip shows the site of surgical removal of the femoral neck in total hip arthroplasty.

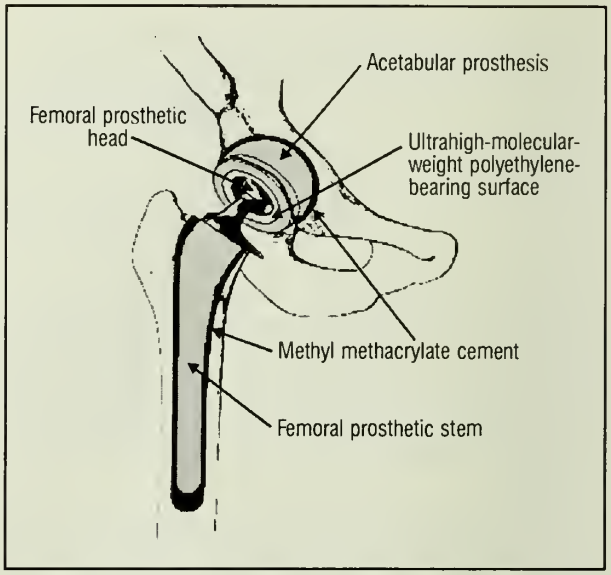

Figure 2.—A total hip arthroplasty with the use of methylmethacrylate cement to fix the prosthetic femoral and acetabular components to the bony structures is shown.

Patients may harbor unrealistic expectations of the degree of activity the prosthesis will safely allow. In preoperative consultation, physicians must stress that the primary goal of the operation is the relief of pain when other options have failed. Motion may be improved, but not in every patient. Most important, heavy repetitive impact loading with activities such as running or jumping may predispose the prosthesis to wear and loosening, thus shortening its life span.

Biomechanics and Materials

During normal ambulation, the human hip undergoes cyclic loading that can place forces three to five times those of body weight on prosthetic components. During more strenuous activity, such as running or climbing, the joint is exposed to much greater forces—as much as 12 times those of body weight. Biomechanical analysis of these forces has prompted design engineers to position the prosthetic components to maximize support of the implant throughout the walking cycle. In general, implants are designed to closely approximate the function of the natural hip joint. Many considerations in materials and manufacturing technology dictate design requirements in prosthetic components that may limit the achievement of this goal, however.

Most hip prostheses consist of an ultrahigh-molecular-weight polyethylene acetabular cup and a metal-alloy femoral component. In cemented techniques, polymethylmethacrylate cement is used to fix the femoral component in bone, whereas in uncemented arthroplasties, the prosthesis interfaces with bone directly. In current practice, acetabular components are rarely cemented, even if a surgeon chooses to fix the femoral component with cement. Uncemented acetabular components are fixed to the pelvis by bone ingrowth into an outer porous metal shell that surrounds the polyethylene cup.

Acetabular Component

In the past decade, ultrahigh-molecular-weight polyethylene has been introduced to replace high-density polyethylene because of its superior resistance to wear.[8] Before Charnley's work, metal acetabular cups were used to articulate directly with metal femoral heads (as in the McKee-Farrar and Ring prostheses). The drawback to this design was the high friction between the two metal surfaces, resulting in wear and loosening of the prosthesis due to high frictional torque. Although Charnley's use of high-density polyethylene reduced these problems considerably, the search for even more wear-resistant, biocompatible materials continues.

Femoral Component

The primary goal in the manufacture of femoral components is to ensure long-term biocompatibility and high resistance to the repeated cyclical loads encountered during normal hip function. The most common metals that have been used in the femoral component are alloys of stainless steel, titanium, and cobalt-chrome. Although cobalt-chrome designs have proved successful for many years, titanium implants are also commonly used. The proponents of titanium cite the fact that it is the most biologically inert of these metals and that its relatively low elastic modulus most closely resembles that of femoral cortical bone.[9]

An innovation in the design of femoral components has been the introduction of separate modular cobalt-chrome heads that are fixed to the neck portion of the femoral stem by interference fit. A choice of different neck lengths in the head component permits accurate adjustment of soft-tissue tension and leg length. Ceramic has been introduced recently as an alternative material for the femoral head component. In in vitro testing, certain ceramics demonstrate a substantially lower coefficient of friction against polyethylene compared with cobalt-chrome alloys. In clinical practice, modular ceramic head components fitted to metal femoral stems have been used by some surgeons in place of cobalt-chrome head components. The comparative long-term efficacy of ceramic heads is not yet known, and some concern has been expressed over the possibility of brittle failure of ceramic components.

Cement

Polymethylmethacrylate cement is a self-curing acrylic polymer without any adhesive properties. It is used as a grouting agent to securely fix the prosthetic components to bone. The polymer achieves fixation through processes known as "microlocking" and "macrolocking." During microlocking, the cement squeezes into the interstices of the cancellous bone to ensure fixation throughout the whole bone-cement interface. In the process of macrolocking, the cement enhances fixation by filling large irregular spaces within the bone surrounding the implant.

The technique of cement implantation has been of great importance in assuring good long-term fixation. Care is taken to ensure proper penetration of cement into the bone and adequate filling of all empty spaces adjacent to the surface of the prosthesis. This is achieved by introducing the cement under pressure. Either intraoperative centrifugation or preparing the cement mixture in a vacuum serves to remove air bubbles during the early stages of polymerization. Bubbles that remain in the cement once it has cured may act as weak spots, or stress risers, that facilitate the propagation of cracks in the cement mantle. In some circumstances, the cement is impregnated with antibiotics to reduce the incidence of postoperative infection. Not all surgeons favor this option because some studies have shown that antibiotic additives may weaken the polymer. Others have expressed the concern that routinely using antibiotics in this manner may contribute to increased drug resistance of certain bacteria.[10]

Cemented Total Hip Arthroplasty

Conventional cemented total hip arthroplasty dramatically improves a patient's function and quality of life. The original Charnley hip arthroplasty provided a good to excellent clinical result in 80% to 85% of patients observed for at least 15 to 20 years. The clinical failures, such as symptomatic aseptic loosening leading to revision arthroplasty, occur at a rate of about 1% per year of follow-up. Radiographic loosening occurs at twice that rate, affecting a third of hip recipients by 15 years.[11] With contemporary prostheses and modern cementing techniques, the rate of femoral loosening appears to be substantially reduced.[12] Regardless of the cementing technique, mechanical loosening occurs more commonly in young, heavy, active men and with certain prosthetic designs.

In patients with rheumatoid arthritis, the clinical failure rate of total hip arthroplasty, which may be as high as 25% at 12 years, is generally higher than in those with osteoarthritis. In patients with rheumatoid arthritis, the incidence of delayed wound healing and sepsis may be increased as well.[13] These patients tend to be younger and to have osteoporosis. In patients with Paget's disease, total hip arthoplasty is usually associated with a satisfactory result, although excessive bleeding from hypervascular bone may complicate the surgical procedure. Total hip arthroplasty may be the only viable treatment alternative in patients with advanced avascular necrosis; some investigators have reported inferior long-term results in these patients, presumably because of their younger age and increased physical demands. In patients with ankylosing spondylitis, total hip arthroplasty is associated with a higher incidence of heterotopic ossification; preexisting soft-tissue contractures may limit hip motion postoperatively.

An important cause of clinical failure leading to surgical revision in cemented total hip arthroplasty is biologic loosening due to aggressive osteolysis.

Phagocytosis of metal, polyethylene, and acrylic wear-debris particles by macrophages leads to localized resorption of bone, with consequent loosening of the prosthetic components. The process is characterized histologically by the presence of macrophages, multinucleated giant cells, and by intracellular particles of cement and polyethylene. On radiographic examination, bone resorption is seen as progressively enlarging lytic foci around the prosthetic components. Mechanical loosening of the device ultimately occurs, occasionally with further fragmentation of the cement surrounding the components.[14] Similar lytic bone resorption may take place in cementless arthroplasties due to debris produced by wear of the femoral head against the polyethylene acetabular component.

Noncemented Total Hip Arthroplasty

Noncemented total hip arthroplasty was developed in response to evidence that cement debris plays an important role in promoting bone lysis and loosening. Prosthetic devices have been developed that achieve fixation without cement either by "press-fit" or by biologic ingrowth. With the press-fit technique, stabilization is achieved by interference fit of the implant into the femur. With biologic ingrowth, fixation occurs by bone ingrowth into a porous surface. Noncemented devices are most frequently used in young patients with high physical demands where a revision surgical procedure in the future will be more likely. Preliminary data suggest that noncemented total hip arthroplasties have a relatively low revision rate and excellent prosthetic durability for as long as 15 years. Compared with cemented hip arthroplasties, however, patients have a higher incidence of low-grade, temporary thigh pain. Although short-term results appear to be less satisfactory compared with cemented hip arthroplasty, after 5 to 20 years, the results in the two procedures are similar.[15] As mentioned, despite the absence of cement debris in noncemented total hip arthroplasties, femoral osteolysis may still occur in as many as 5% of patients as a result of the formation of polyethylene wear debris. Noncemented total hip arthroplasty, whether of the press-fit or biologic ingrowth variety, requires a more exacting surgical insertion technique than does cemented arthroplasty because maximum contact between prosthesis and bone must be achieved. Even in the best of circumstances, complete contact may be difficult to achieve. Some manufacturers have dealt with the problem by creating a variety of implants to better match the various internal shapes and sizes of different femurs. Unfortunately, this approach creates a logistical and cost problem because of the large inventory of implants that must be kept available.

The biologic ingrowth designs are now used extensively. Studies of animals have shown excellent ingrowth of bone into the porous surfaces of both cobalt-chrome and titanium implants. One method used to produce a porous ingrowth surface in cobalt-chrome prostheses is to fuse metal beads 250 to 400 μm in diameter onto the surface of implants. Small pores are present between the beads. Studies have shown that bone ingrowth into porous surfaces begins within the first 6 to 12 weeks after implantation.[16] Implant-retrieval studies in humans have confirmed that ingrowth of bone and fibrous tissue does occur. Even in prostheses shown radiographically to be well fixed, however, a surprisingly low percentage of available surface area is involved with the ingrowth of bone. Despite concerns about how much ingrowth actually takes place, clinical studies have shown that some noncemented porous-ingrowth designs are as successful as cemented implants.

Some investigators have cautioned that metal ion release from the porous coating of the prosthesis may cause an osteolytic reaction in adjacent bone.[17] Others have suggested that bone fixation can be enhanced by coating the implant with hydroxyapatite or tricalcium phosphate, both of which closely resemble natural bone mineral. These agents may further serve as a barrier to elemental ion transfer from the prosthetic device into the surrounding tissues.[18]

Because early reports noted an increased rate of acetabular loosening relative to femoral loosening in cemented arthroplasties, the concept of the "hybrid" total hip arthroplasty has been adopted by many surgeons. The hybrid total hip arthroplasty consists of a cemented femoral stem and a noncemented acetabular cup. Cementing the stem using contemporary techniques allows earlier unrestricted weight bearing and yields a lower incidence of low-grade thigh pain. Leaving the acetabular component uncemented avoids the consequences of cement fragmentation and loosening. In many centers, hybrid total hip arthroplasty is now the preferred technique for primary hip arthroplasty in patients older than 60. Results in patients observed for two to four years show that the hybrid arthroplasty performs as well as cemented total hip arthroplasty in the short term.[19]

Operative Aspects

As with any major surgical procedure, cardiovascular, renal, and pulmonary function must be fully assessed preoperatively in all patients undergoing total hip arthroplasty. The procedure may be done under regional as well as general anesthesia, allowing patients with medical contraindications to general anesthesia to undergo it.[2] Total hip arthroplasty is contraindicated if active infection is present either locally in the pelvic region or elsewhere in the body. The procedure may be performed through various surgical approaches, and in all techniques, scrupulous precautions are taken to prevent bacterial contamination of the open wound. Prophylactic intravenous antibiotics are used routinely. To reduce the chance of infection further, some surgeons advocate added precautions such as operating in laminar-flow enclosures with filtered air or wearing special hoods designed to divert exhaled air from the operative field.

Early Complications

Fracture

The incidence of fracture is about 1%[20] and has been reduced with the use of modern prostheses and contemporary surgical techniques. A greater incidence of fractures (6%) occurs in revision arthroplasties with noncemented prostheses. The femur is the most common site of fracture during both primary and revision procedures. Fractures of the acetabulum and pubic rami occur only rarely.

Nerve injury. Transient or permanent nerve injury may occur with total hip arthroplasty. The most common nerve injured is the sciatic, where the incidence is reported to be about 0.7%.[21] This is usually caused by intraoperative trauma, but can also complicate postoperative dislocation of the prosthesis. The prognosis for nerve recovery is good unless the nerve is severely damaged. Operative trauma results in less frequent injury to the obturator, gluteal, and femoral nerves.

Dislocation. Dislocation of the femoral head component out of the acetabular socket occurs in 1% to 3% of primary total hip procedures. The main causes of dislocation include inadequate patient compliance with postoperative precautions and malposition of the prosthetic components at the time of the operation. Dislocation is second only to loosening as a cause of revision.[20] The most common technical error predisposing to dislocation is malposition of the acetabular component. Most dislocations occur within six months of the surgical procedure, and most patients may be managed conservatively. Recurrent dislocations may require surgical revision, however.

Deep vein thrombosis and pulmonary embolism. Much attention has been paid to deep vein thrombosis and pulmonary embolism as a leading cause of morbidity and mortality in patients with total hip arthroplasty. In the absence of prophylaxis, the incidence of deep vein thrombosis may be as high as 70% and of pulmonary embolism, 20%. Mortality from pulmonary embolism has been reported to be as high as 2%.[22] Routine prophylaxis against deep vein thrombophlebitis is therefore recommended in total hip arthroplasty. Graded-compression elastic stockings and early mobilization are used as minimum precautions. Various anticoagulation regimens have been administered, but investigators do not agree as to which is most effective. Low-dose heparin is commonly used, but is reported to be of questionable benefit unless combined with antithrombin III.[23] Low-dose warfarin is used in many centers; but many surgeons are reluctant to accept the risk of bleeding complications that may occur with this and other regimens. Using regional anesthesia in total hip arthroplasty is reported to decrease the incidence of deep venous thrombosis and pulmonary embolism by as much as two thirds when compared with general anesthesia.[24] Because thromboembolism may occur despite prophylaxis, vigilance is necessary, and clinical suspicion of this complication may well prompt Doppler ultrasound examination, leg venography, pulmonary scanning, or pulmonary angiography.

Wound Complications

The most noteworthy wound complications in total hip arthroplasty are hematoma and infection. The overall incidence of hematoma is 3.5%.[20] Infection may occur as a secondary complication because the hematoma may act as a culture medium for bacteria. Superficial wound infections are rare and must be differentiated from deep infection involving the prosthetic components themselves.

Late Complications

Infection

Most studies report an infection rate of 1% or less in primary total hip arthroplasty. In revision arthroplasties this rate is reported to be 3% or higher. Infections diagnosed within the first few weeks after the procedure or as long as a year later are most likely due to perioperative contamination.[25] This relatively low infection rate is due in part to the routine use of prophylactic antibiotics in the perioperative period. Antistaphylococcal drugs such as vancomycin or one of the cephalosporins are used most frequently for this purpose. The additional use of ultraclean air enclosures may reduce infection rates to lower than 1%. As noted earlier, another prophylactic technique adopted by some surgeons is the direct addition of antibiotics to cement, which allows the drug to elute into the adjacent tissue. Although some use this technique routinely, others reserve its use for hips that have been previously infected. By combining different prophylactic strategies during total hip arthroplasty procedures, some report an incidence of deep infection as low as 0.4%.[26]

Deep infection in total hip arthroplasty that presents more than a year after the procedure may occur as the result of hematogenous seeding of the implant by organisms originating from a distant site. Infections of the skin, urinary tract, gastrointestinal tract, and mouth are most frequently implicated as sources. Because of this phenomenon, patients who have undergone total hip arthroplasty are counseled to seek rapid treatment of any suspected bacterial infection. Routine prophylactic antibiotic treatment is also recommended for any invasive procedure that could result in a hematogenous spread of bacteria.

Established deep infection in these cases has a tendency to persist unless all prosthetic material is removed, infected tissues are thoroughly debrided, and appropriate antibiotic treatment is administered. Some surgeons have advocated immediate reimplantation of another prosthesis at the time of the initial debridement. Most defer such revisions for 3 to 12 months, however, and proceed only if the infection appears clinically quiescent. Subsequent hip aspirates must be culture-negative before revision arthroplasty is attempted.

Heterotopic Ossification

Heterotopic ossification may occur in as many as 70% of patients undergoing total hip arthroplasty. The incidence of this complication in its more severe and limiting form is much less—only about 4%.[27] When severe, heterotopic ossification usually compromises range of motion rather than producing pain. Patients at risk include those with previous heterotopic bone formation and those with diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, or in men, hypertrophic osteoarthritis. Prophylaxis with certain nonsteroidal anti-inflammatory drugs or with postoperative low-dose radiation therapy is effective for those patients who are at risk. In the event that substantial ossification develops, surgical excision may be helpful, but it is usually delayed for a year to allow the ectopic bone to mature fully.

Loosening

Loosening is the most common cause of failure in noninfected hip arthroplasties. It is manifested by absorption of bone around the implant or cement and is usually detected radiographically before the patient has pain. Loosening may be mechanical or biologic in nature and frequently occurs with long-standing infection. Mechanical loosening results from loading that exceeds the strength of either the prosthetic material or its interface with bone. Excessive loading because of overuse, poor prosthetic design, and improper insertion technique may predispose to this problem. Biologic loosening results from bone resorption mediated by cells stimulated by the presence of particulate-wear debris from cement, polyethylene, or metal. Poor cementing technique, common in earlier years, has been implicated as a cause of loosening. In one study, the incidence of aseptic loosening using first-generation cementing techniques was 32% at 15-year follow-up, with a revision rate of 12.7% as a consequence.[28] More recent studies in which newer, second-generation cementing techniques have been used show reduced loosening rates.

Future Directions

Total hip arthroplasty is continuously evolving in terms of materials, prosthetic design, surgical technique, prevention of complications, and postoperative management. The future of prosthetic hip design lies in the development of new materials that will have acceptable biocompatibility and better physical properties, leading both to better integration into bone and to better wear characteristics. One direction in design research is the development of an isoelastic prosthesis, which has physical properties similar to bone. To achieve this, some researchers have experimented with composites of plastics and metals, elements that can confer flexibility and strength at the same time.[29] Research in the area of noncemented ingrowth prostheses is focusing on designs that will permit greater bony ingrowth to produce better short- and long-term fixation. Finally, research is underway to identify better materials for the bearing surfaces of prosthetic components to eliminate wear particle-induced osteolysis.

Custom-made prostheses designed to improve individual fit have received attention in recent years. The goal of a precise prosthetic fit is to lower the incidence of postoperative discomfort in noncemented total hip arthroplasty and to provide better survival of the arthroplasty. Because of the high cost of materials and engineering, economics will limit the development of these types of devices. Improvements in technology may allow custom implants to be produced more cheaply, however.

New limitations in health care reimbursement by third-party payers are beginning to have an effect on the economics of total hip arthroplasty. Most of the cost of primary total hip arthroplasty is determined by the length of a patient's hospital stay and by the cost of the prosthetic implant. In our institution (University of California, San Francisco, Medical Center), hospital stays for primary total hip arthroplasty that used to range from 10 to 14 days are now being reduced to 5 to 7 days. Efforts are underway to reduce the cost of prosthetic implants both by limiting the types of implants being used and by reducing the unit cost of implants through contracts with vendors based on volume use.

In an era in which increasing attention is being paid to the relative benefits of medical services, outcome studies are being undertaken to document the results of procedures such as total hip arthroplasty. A prospective study in Canada has shown conclusively, from a public health perspective, that both cemented and uncemented total hip arthroplasty are cost-effective and beneficial.[30] Similar studies will no doubt be required in this country, both to assess results of new arthroplasty techniques and to monitor the quality of care provided to patients with total hip arthroplasty whose treatment is increasingly affected by cost reduction policies.

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Conferences and Reviews

A 15-Year-Old Girl With Acute Renal Failure
Clinicopathologic Conference

Discussants

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This discussion was selected from the weekly Grand Rounds in the Department of Pediatrics, University of California, San Diego, School of Medicine.

Case Presentation

VIVIAN M. REZNIK, MD: The patient, a 15-year-old girl, was admitted to University Hospital, San Diego, California, because for two months she had had nausea, vomiting, and malaise. Although the results of a routine urinalysis a year before her presentation had been normal, a urinalysis done by her private physician before admission showed 2+ glucose, 2+ protein, and numerous leukocytes. There was no history of recent analgesic or antibiotic administration.

On physical examination she was thin, pale, pubertal, and appeared chronically ill. Her weight was 46 kg (101 lb), height 63 cm (5 ft 3 in), and blood pressure 130/80 mm of mercury. She had shotty left anterior cervical nodes. On examination of her abdomen, her liver could be palpated 2 cm below the right costal margin. The spleen tip was palpable on deep inspiration. Her extremities showed no edema.

Laboratory values obtained on admission were as follows: serum sodium 139, potassium 3.3, chloride 102, and bicarbonate 16 mEq per liter; calcium, 2.50 mmol per liter (10.0 mg per dl); phosphorus, 2.07 mmol per liter (6.4 mg per dl); uric acid, 506 μmol per liter (8.5 mg per dl); cholesterol, 4.40 mmol per liter (170 mg per dl); and glucose, 5.1 mmol per liter (92 mg per dl); liver function test values were normal. Blood urea nitrogen concentration was 41.1 mmol per liter (115 mg per dl), and serum creatinine level was 610 μmol per liter (6.9 mg per dl). A urinalysis showed a specific gravity of 1.016, pH 6.0, 2+ protein, 1+ glucose, 0 to 50 leukocytes per high-power field, 0 to 2 coarse granular casts, and 2 to 5 granular casts.

Urine chemistry levels were as follows: sodium, 59 mmol per day (59 mEq per 24 hours); and potassium, 35 mmol per day (35 mEq per 24 hours). A complete blood count elicited the following values: hemoglobin, 84 grams per liter (8.4 grams per dl), hematocrit, 0.24 (24%); mean corpuscular volume, 82 fl (82 μm^3); mean corpuscular hemoglobin, 29 pg; mean corpuscular hemoglobin concentration, 350 grams per liter (35 grams per dl); leukocyte count, 13.7×10^9 per liter (13,700 per mm^3) with a normal differential; platelet count, 650×10^9 per liter (650,000 per mm^3); and erythrocyte sedimentation rate (ESR, Westergren), 125 mm per hour. A creatinine clearance was 0.15 ml per second (9 ml per minute) per 1.73 m^2, and the 24-hour urine protein excretion was 0.66 grams (660 mg). Total hemolytic complement and C3 complement levels were normal; an antinuclear antibody test was negative. A purified protein-derivative skin test was negative. Chest x-ray and hand films were normal. An intravenous pyelogram (IVP) with tomography showed decreased uptake with normal kidney size (right kidney 12.7 cm, left kidney 13.0 cm; normal, ± 2 standard deviations = 11.8 ± 3.0 cm) and no signs of obstruction. Cultures of blood and urine were negative for bacterial or viral pathogens.

Differential Diagnosis

MONICA RIECKHOFF, MD: This is an interesting case of a 15-year-old female adolescent with renal failure that raised several perplexing issues. The first problem was to determine whether her renal failure was acute or chronic. The next question was whether prerenal, renal, or postrenal effects (or all three) were to blame. Finally, if her problem was intrarenal, were there any clues about what disease process was occurring?

First, we should consider the time course of her renal failure. Did she have acute renal failure, acute worsening of chronic renal failure, or chronic renal disease? Differentiating among these is important to target possible causes.

This patient was young and would be expected to tolerate a substantial reduction in renal function before presenting with uremic symptoms such as nausea, vomiting, and malaise. These symptoms tend to occur when the glomerular filtration rate is less than 5% to 10% of

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ABBREVIATIONS USED IN TEXT

ESR = erythrocyte sedimentation rate
IVP = intravenous pyelogram

normal. Her creatinine clearance was about 10% of normal, which would overestimate her glomerular filtration rate because there is tubular secretion of creatinine. Patients, particularly children with chronic renal failure, may tolerate a blood urea nitrogen concentration of greater than 35.7 mmol per liter (100 mg per dl) and a serum creatinine concentration of greater than 884 μmol per liter (10 mg per dl) without symptoms.

Another helpful piece of information was her normal urinalysis one year before she was seen. Although not conclusive, it suggests that she had no severe dysfunction of her kidneys at that time. The pronounced degree of renal failure less than a year later suggests a fairly rapid process.

The patient was well until two months before presenting and, although appearing chronically ill, had only a mild discrepancy between her height (40th percentile) and weight (20th percentile), suggesting mild weight loss without notable effect on stature.

Looking at her laboratory data, a normal potassium level could have several explanations: There was time for renal and extrarenal adaptation, anorexia had resulted in decreased potassium intake, or a renal defect exists in potassium handling. An elevated phosphorus level with normal calcium values and no evidence of renal osteodystrophy on roentgenography suggests insufficient time for compensatory hyperparathyroidism or altered vitamin D metabolism, which is seen in patients with chronic disease. Normocytic anemia could be found in acute renal disease from hemolysis, as seen in patients with the hemolytic-uremic syndrome, renal vein thrombosis, or systemic lupus erythematosus. It would have been helpful to know if there was evidence of hemolysis on the smear with burr cells, helmet cells, or schistocytes and to obtain a reticulocyte count. In addition, several systemic diseases associated with acute renal failure cause nonhemolytic normocytic anemia. In patients with chronic renal disease, anemia is caused by decreased erythropoietin production and the increased erythrocyte destruction that can result in hematocrits of 0.20 to 0.25 (20% to 25%), but this usually takes place over a period of months. Finally, the finding of normal rather than small kidney size on IVP suggests a more acute process. Normal-sized kidneys, however, can be seen in chronic diseases such as polycystic kidney disease, amyloidosis, and scleroderma. Although the patient presents a mixed picture, the findings suggest a relatively acute process and the possibility that her nausea, vomiting, and malaise were due to an underlying disease rather than uremia.

The next issue is whether there is evidence of prerenal or postrenal causes of renal failure. Prerenal disorders include problems with renal perfusion from cardiac failure, volume depletion, shock, or renovascular disease. We are missing some key pieces of information in the patient's physical examination, and I assume their absence reflects their normality. These include her pulse, temperature, or signs of heart failure (liver down 2 cm, but no jugular venous distension or edema). More details on her mental state and perfusion would have been helpful. She was not hypotensive. Patients with prerenal disorders typically present with a low fractional excretion of sodium whereas those with acute tubular necrosis or tubulointerstitial disease present with an increased fractional excretion of sodium, as seen in this patient. Prerenal factors, therefore, seem unlikely to be playing a major role. Postrenal causes are safely ruled out by the lack of obstruction on IVP.

How was the renal parenchyma involved? Her urinalysis showed glucosuria, suggesting tubular dysfunction. The proteinuria—0.66 grams per day (660 mg per 24 hours)—is notable, but is not in the nephrotic range. A normal cholesterol level and lack of edema also are against the nephrotic syndrome. A serum albumin level might have been helpful. The proteinuria could be due to tubular or glomerular dysfunction. Electrophoresis of the urine might show low-molecular-weight proteins, suggesting isolated tubular dysfunction. The leukocytes in the urine could be from a urinary tract infection, glomerular disease—either proliferative or inflammatory—or tubulointerstitial disease and can be seen in rare cases of urolithiasis or tumor. Staining for eosinophils would have been helpful to evaluate for acute interstitial nephritis, particularly from medications. The absence of hematuria makes glomerulonephritis less likely. Granular casts that consist of coarse or fine particles embedded in hyaline matrix are seen in normal healthy persons, but can be seen in persons with chronic lead intoxication, dehydration, glomerulonephritis, and tubulointerstitial disease. The patient has acidosis with an increased anion gap, which could be from lactate, ketoacids, salicylates, ethylene glycol or methanol ingestion, or simply uremia with a decreased ability to excrete organic acids. There are insufficient data to exclude renal tubular acidosis or Fanconi's syndrome, which over time can cause renal failure through secondary complications such as nephrocalcinosis.

An interesting point is that the patient's degree of renal insufficiency is more severe than commonly seen in patients with isolated tubular disease in whom tubular dysfunction is usually more prominent than the reduction in the glomerular filtration rate. There is no history of polyuria or nocturia to suggest tubular concentrating problems. The IVP showed decreased uptake, which could be from glomerular or tubulointerstitial disease, with pressure backing up because of luminal obstruction. Overall, the picture suggests substantial tubulointerstitial disease, but glomerular disease cannot be excluded.

Her history includes some other important information. She had two months of nausea, vomiting, and malaise, which may simply be from her azotemia or

could be from another underlying illness. In addition, she had borderline hypertension (90th to 95th percentile), shotty cervical adenopathy, possible hepatosplenomegaly, a markedly increased sedimentation rate, mildly elevated leukocyte count with a normal differential, pronounced normocytic anemia, and normal liver function test values.

The differential diagnosis of acute renal failure is extensive in this patient, given her nonspecific presenting features. Developmental abnormalities such as cystic disease, renal hypoplasia, or dysplasia are ruled out by a normal IVP. Tumors can cause renal disease through direct invasion of the kidney, but enlarged or distorted kidneys would be expected to be seen on IVP. Tumors such as lymphoma would certainly explain this patient's associated symptoms, hepatosplenomegaly, and laboratory findings. Also, an immune response to tumor antigen can cause disease, but most commonly it causes membranous glomerulopathy or, in the case of lymphoma, minimal change disease. Uric acid nephropathy occurs most commonly in patients being treated for malignant neoplasms, and this patient's uric acid level is only mildly elevated.

Metabolic diseases commonly affect the kidneys. Many of these diseases are part of syndromes that include developmental delay and other features not present in this patient.

Acute tubular necrosis certainly causes acute renal failure, but its presence would not explain the two-month history of symptoms and pronounced anemia. Heavy metal poisoning is consistent with her history, and it would be important to probe for any possible exposure, particularly to lead, arsenic, or mercury. A urine screening test for heavy metals should be done. Even more common would be medication-related acute tubular necrosis, but there was no history of medication use.

Intravascular coagulation can result from renal vein thrombosis; however, this is typically seen in infants with sepsis and shock or in children with the nephrotic syndrome or cyanotic heart disease. The kidneys are usually tender and enlarged with gross or microscopic hematuria. Cortical necrosis is seen in patients with the hemolytic-uremic syndrome, but they have thrombocytopenia. This patient has a thrombocytosis. The clinical course in this patient is also not consistent with this diagnosis.

Glomerulonephritis is unlikely given the history and lack of hematuria. Patients with poststreptococcal glomerulonephritis usually have a preceding upper respiratory tract or skin infection one to two weeks before their illness, a low C3 level, and hematuria with erythrocyte casts. The kidneys tend to be enlarged. This diagnosis could be ruled out with antistreptolysin O and streptozyme titers. Another possibility is membranoproliferative disease, but hematuria is usually present, and C3 and total complement levels are reduced in about 40% of patients. Patients with idiopathic rapidly progressive nephritis tend to have edema, gross hematuria, hypertension, anemia, and hypergammaglobulinemia. Acute renal failure often develops after an acute nephritic or nephrotic episode. Finally, membranous glomerulopathy is uncommon in children and usually presents as the nephrotic syndrome. Almost all patients have microscopic hematuria and progress to renal failure over many years. Glomerulonephritis can be due to endocarditis, but this patient had no murmur or history of fevers.

Connective tissue disease is a concern, given the systemic symptoms and increased ESR. Patients with systemic lupus erythromatosus typically have a high ESR and other symptoms such as fever, rash, arthritis, and lung, heart, or central nervous system disease, but occasionally kidney disease may be the only manifestation. It cannot be ruled out, but is unlikely in this patient, given the negative antinuclear antibody test. A lupus erythematosus preparation might also be useful. Juvenile rheumatoid arthritis in a young woman this age would probably present as polyarthritis of the knees, wrists, ankles, or elbows. In addition, there is usually hematuria and the kidneys are enlarged. Scleroderma is a rare disease in childhood, and renal disease occurs primarily in patients with the systemic form, which may antedate skin disease. Progressive renal disease rarely develops. Other autoimmune diseases are unlikely, given the lack of associated symptoms.

Acute tubulointerstitial nephropathy is a category of renal parenchymal disease that best fits the time course and laboratory findings in this patient.[1-3] There are many different causes of this disease.

The use of drugs, particularly nonsteroidal anti-inflammatory drugs, should be considered if there is any history of long-term use. Nonsteroidal anti-inflammatory drugs, unlike other medications causing tubulointerstitial nephropathy, only rarely cause hypersensitivity reactions and hematuria, but edema is usually prominent.

Pyelonephritis is unlikely to be present when cultures are negative. Other systemic infections, however, should be considered.[4] The first cases of tubulointerstitial nephritis associated with scarlet fever occurred in the 1860s. Since then, many other infections have been added to the list. Streptococcal infection is unlikely because the patient's symptoms would be more acute, with evidence of streptococcal infection, and the kidneys are often enlarged.[5] Other diseases that are also unlikely because of their more rapid onset (from days to a few weeks), associated symptoms (such as diarrhea, fever, pneumonia), and typically a travel history or exposure include those caused by *Staphylococcus* species, gram-negative bacilli, typhoid fever, diphtheria, brucellosis, legionellosis, leptospirosis, *Mycoplasma* species, *Campylobacter* species, and endocarditis.[6,7] Many of these could be ruled out by titer or culture.

Viral infections and tubulointerstitial nephropathy were first reported with measles, although these cases were severe, complicated by streptococcal infection, and resulted in death. Epstein-Barr virus infection is a consideration in this patient. Typically, however, patients have a more abrupt onset, with fever, pharyngitis, rash,

adenopathy, and hepatosplenomegaly.[8,9] Her age and other symptoms fit nicely, however. Liver function tests may show mildly abnormal values, and blood tests may show atypical lymphocytosis, hematuria, and hemolytic anemia with a positive Coombs' test and, rarely, thrombocytopenia and agranulocytosis. There are, however, reports of cases without fever, pharyngitis, or atypical lymphocytes and that present over the course of two months. Epstein-Barr virus infection is certainly a concern, and a Monospot test and Epstein-Barr virus titers are warranted. Cytomegalovirus is usually associated with transplantation or other immunocompromise or in infants. Symptoms would be similar to those of infectious mononucleosis with possible hemorrhagic cystitis. A urine test for cytomegalovirus could be done. Infection with the human immunodeficiency virus can involve the kidney with substantial proteinuria, but patients usually have a history of other human immunodeficiency virus-related illnesses.[10] Hantavirus, only recently described here in the United States, presents with fever and hemorrhage. Serum hepatitis has associated arthralgias, arthritis, urticaria, and rash.

Other infections associated with tubulointerstitial nephritis include Rocky Mountain spotted fever, schistosomiasis, and malaria, but these also cause more severe illness and have associated symptoms. Toxoplasmosis is a febrile illness with malaise, cervical adenopathy, hepatosplenomegaly, rash, and uveitis, and systemic disease is usually seen in infants and immunocompromised patients. There is, however, a case of a 10-year-old girl with uveitis and tubulointerstitial nephropathy who was otherwise well.[11] Chorioretinitis is commonly not recognized. Toxoplasmal titers should be checked, and it may be possible to see organisms on renal biopsy. Tuberculosis is possible, despite the negative purified protein-derivative test, if the patient is anergic. The IVP and normal chest roentgenogram, however, are against a diagnosis of tuberculosis. Secondary syphilis is a consideration, although renal involvement is uncommon and usually appears as membranous glomerulopathy.[12] Often patients have a rash (palms and soles), mucous membrane involvement, fever, and arthralgias. A rapid plasma reagin or VDRL test should be done, and it may be possible to find spirochetes on dark-field examination. Fungal disease should be considered but is unlikely in a patient without immunocompromise.

Besides infection, acute tubulointerstitial nephritis can be seen with glomerulonephritis and collagen vascular diseases, which have already been discussed. Necrotizing systemic vasculitis is possible, but polyarteritis nodosa often produces systemic vasculitis with abdominal pain, fever, and hematuria. In patients with small-vessel vasculitis, purpura, fever, and eosinophilia are commonly present.

In patients with hereditary tubulointerstitial nephritis, also called medullary cystic disease and familial juvenile nephronophthisis, the kidneys are small with severe diffuse cortical atrophy and cysts at the corticomedullary junction. Children usually fail to thrive and have polydipsia and polyuria.

Some of the systemic diseases associated with tubulointerstitial nephropathy are more chronic but also possible candidates in this case. Sarcoidosis is a disease of noncaseating granulomas involving the lungs, liver, spleen, bone marrow, and lymph nodes.[13,14] It is more prevalent in African Americans and Hispanics, men, and older patients. Most infected children have hilar adenopathy, hepatosplenomegaly, and cervical adenopathy. Hypercalcemia, modest proteinuria, sterile pyuria, and anemia are common in patients with renal involvement.

Dysproteinemia and neoplasms such as Waldenström's macroglobulinemia are rare in children and would cause associated symptoms, as would cryoglobulinemia. Occasionally tubulointerstitial nephropathy is seen as part of the renal involvement in neoplasms such as lymphoma and leukemia.[15-18] Usually there is an associated glomerulopathy causing a greater degree of proteinuria than was seen in this patient, but it should be included in the differential diagnosis.

Finally, idiopathic tubulointerstitial nephritis can be associated with anti-tubular basement membrane antibody or immune complexes and also a syndrome of the disorder with uveitis. This syndrome was first described in 1975 and occurs in young women with similar systemic complaints as in this patient, anemia, and an elevated ESR.[19-21] Abdominal pain, muscle pains, fever, and kidney enlargement with substantial hypertension are sometimes present. On biopsy, besides the usual findings of tubulointerstitial nephritis, noncaseating granulomas can rarely be seen. Granulomas may also be found in the bone marrow. The uveitis usually does not appear for weeks to months after the renal disease.

Given the patient's nonspecific presenting features, many of the diseases mentioned could account for her relatively rapid renal failure, two-month history of nausea, vomiting, and malaise, anemia, and elevated ESR. It would be helpful to know by ultrasonography if she has hepatosplenomegaly. Considering the patient's age and sex, the syndrome of tubulointerstitial nephropathy with uveitis makes the best fit, and I would be concerned that uveitis may develop. Previously mentioned diseases must be ruled out and a renal biopsy obtained.

Clinical Diagnosis

Acute interstitial nephritis.

Clinical Course and Discussion

The diagnosis was not clear to the clinicians caring for this child. A bone marrow aspiration showed only myeloid hyperplasia. A gallium scan demonstrated intense uptake in the kidneys and several areas of abnormal uptake in lymph nodes. Biopsy specimens of a left scalene node and a right femoral node both showed a nodular tumor with a mixture of lymphocytes and large atypical histiocytes that were compatible with Reed-Sternberg cells. An initial diagnosis of nodular sclerosing Hodgkin's lymphoma was made. The patient under-

went exploratory laparotomy for staging and a kidney biopsy. Tumor nodules were seen on sections of abdominal lymph nodes, liver, and spleen. There were no nodules on the surface of the kidneys. There was no ureteral obstruction. The histologic findings were considered consistent with a mixed-cellularity type of Hodgkin's lymphoma, stage IVB.[22]

Light microscopy of the kidney showed diffuse infiltration of lymphocytes and plasma cells throughout the interstitium. The glomeruli showed a mild increase in mesangial matrix. Immunofluorescence studies of the kidney showed irregular, segmental, granular deposition of complement C3 in the mesangial region of most glomeruli.[22]

A regimen of intravenous hydration and chemotherapy was begun. The patient received methotrexate, vincristine sulfate (Oncovin), and procarbazine hydrochloride with daily oral prednisone (MOPP). After the first two weeks, her blood urea nitrogen concentration was 8.6 mmol per liter (24 mg per dl), and the serum creatinine concentration was 160 μmol per liter (1.8 mg per dl). Monthly chemotherapy with the same agents was continued for six months. At that time, her urea nitrogen concentration was 6.8 mmol per liter (19 mg per dl), serum creatinine 70 μmol per liter (0.8 mg per dl), and the results of a urinalysis were normal. The IVP was repeated and was normal, showing reduced renal size. A kidney biopsy was again done and showed a pronounced decreased interstitial infiltrate. She was treated with monthly courses of chemotherapy for a total of 18 months. After this, she received vinblastine sulfate weekly for two years. She has been in remission for 12 years, and her renal function remains normal.

This was an unusual case of lymphoma presenting as acute renal failure. Malignant neoplasms can present as acute renal failure, acute glomerulonephritis, the nephrotic syndrome, or asymptomatic nephromegaly.[15-18,23-25] Pathologic disorders include minimal change nephrotic syndrome, membranoproliferative glomerulonephritis, and membranous glomerulonephritis. This case was unusual because there was direct infiltration of the interstitium, causing a mixed presentation of both glomerular and tubular abnormalities. The disease responded quickly and completely to chemotherapy, and the patient has done remarkably well over a long period of time.

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Epitomes

Important Advances in Clinical Medicine

Neurosurgery

John H. Neal, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association, and the summaries were prepared under the direction of John H. Neal, MD, and the panel.

Stereotactic Neurosurgery for Parkinson's Disease

The development of effective pharmacologic treatment of Parkinson's disease in the 1950s led to a dramatic decline in the use of stereotactic procedures for this disorder. The growing population of patients with Parkinson's disease, however—40,000 newly diagnosed per year—has resulted in a large group of patients who either are refractory to medical therapy or have unacceptable side effects. Coupled with new neuroimaging and treatment techniques, this accounts for a recent rekindling of interest in stereotactic neurosurgery for movement disorders. Imaging techniques of magnetic resonance imaging (MRI) and computed tomography (CT) allow more accurate locating of the lesion site and the production of smaller, less morbid lesions. At the same time, refinements in techniques of operative stimulation and recording have provided assurance of the physiologic accuracy of these targets. The availability of ultrashort-acting anesthetic agents has allowed efficient sedation during the mechanical portions of these procedures while retaining an awake, cooperative, and comfortable patient during the physiologic testing. The resulting improvement in patient comfort and blood pressure control has added to the safety of this procedure. These refinements have resulted in long-term efficacy for reducing tremor, documented in blinded studies, and a one- to three-day hospital stay.

The recent realization that CT (and perhaps MRI) could replace ventriculography has resulted in the ability to identify lesion sites in relation to surrounding healthy structures. For example, one of the most common lesion sites is the ventralis intermedius nucleus of the thalamus, which is adjacent to the internal capsule. Identifying the internal capsule with CT allows the preservation of this structure in those patients in whom standard coordinates would otherwise put the lesions too far lateral. This has decreased the risk and heightened accuracy because ventriculography itself may both distort and displace the third ventricle and the resulting lesion coordinates. Careful stimulation of an awake patient to verify position is still necessary; the overall morbidity is 8%, with a long-term cure rate for tremor of 80% to 93%.

The results of ventralis intermedius thalamotomy for tremor are impressive, with the need for medication and susceptibility to its adverse effects being reduced. Gait difficulty and bradykinesia, however, which are often the most disabling features of Parkinson's disease, are not affected by thalamotomy.

Because of this major limitation, pallidotomy has been making a comeback as a surgical treatment of Parkinson's disease. In this procedure, the posterior portion of the globus pallidus, rather than the ventralis intermedius, is selectively ablated. Motivated both by the mounting evidence of the importance of pallidal output in producing the symptoms of Parkinson's disease and the singular success of early experience with pallidotomy, investigators have shown that lesions in this target can substantially improve all three of the cardinal signs of Parkinson's disease. Tremor was reduced in 81% of patients in a recent series, rigidity and bradykinesia lessened in 92%, and gait was improved in most patients. The leg pain sometimes seen in these patients was relieved, and, remarkably, bilateral clinical improvement was seen in 75% of patients receiving unilateral lesions. The technical aspects of producing this lesion are similar to those of thalamotomy, although unlike the immediate response in the latter, symptom relief may require several days or weeks. An important drawback of pallidotomy is a 7% to 14% risk of postoperative visual field deficits that can occur because the lesion must be placed near the optic tract. Although some of these defects are minor, careful patient counseling is essential, and thalamotomy remains the procedure of choice when tremor is the predominant symptom.

On the horizon are such techniques as thalamic stimulation, offering almost 90% efficacy for tremor without the risk of an ablative lesion. Further advances in stereo-

tactic technique, neuroimaging, and our understanding of the pathophysiologic processes of Parkinson's disease are likely to lead to improved efficacy and lessened risk in the surgical management of intractable movement disorders.

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Cardiac Bypass and Hypothermia in the Treatment of Complex Aneurysms

ALTHOUGH EARLY CLINICAL experience with closed-chest bypass using hypothermia demonstrated its technical feasibility in the 1960s, this combination of techniques added considerably to the morbidity and mortality associated with the repair of cerebral aneurysms. In particular, postoperative intracranial hemorrhages accounted for a substantial portion of the morbidity and mortality.

The procedure was used sporadically over the next ten years with intermittent success. During that time, dramatic improvements in bypass pump-oxygenator technology, as well as advances in anesthetic techniques, helped to reduce the incidence of complications noted by earlier studies. These changes, a better understanding of physiology, and more experience with correcting the coagulopathy after the procedure led to the increased use of this treatment for complex intracranial aneurysms. During the 1980s, studies using hypothermic bypass with cardiac standstill documented distinct advantages for the management of giant aneurysms in previously inaccessible locations. These advantages included eliminating the risk of rupture during final dissection and enhancement of the ability to manipulate the aneurysmal sac during circulatory suspension. Using circulatory arrest improves visualization by collapsing the aneurysmal sac. This enhanced visualization allows for more accurate clip placement on many aneurysms with difficult necks. Furthermore, the technique allows surgeons to do an endarterectomy of the aneurysm when necessary for better clip closure.

In addition to these advantages, studies have shown this method to be practical for treating complex aneurysms, with a 93% rate of aneurysm occlusion, a permanent morbidity rate of 13.3%, and a 6.7% mortality. Several studies of this combination of techniques have shown good or excellent results in 73% of patients treated. This compares favorably with the best results without hypothermic cardiac standstill, a 39% occlusion rate for giant basilar aneurysms, with a 23% permanent morbidity rate and a 25% mortality.

Because hypothermic cardiac standstill represents additional risks not normally associated with microsurgical clipping of an aneurysm, the selection of appropriate patients is critical. Only patients with complex aneurysms in locations that are difficult to reach are considered candidates for hypothermic cardiac bypass with standstill. Throughout the past 30 years, the definitions of complex and inaccessible aneurysms have changed dramatically as a result of the introduction of the operating microscope and a host of new surgical techniques and approaches. Aneurysms of the anterior communicating artery complex, once thought inaccessible, are now routinely clipped using these techniques, with a low incidence of morbidity and infrequent fatalities. Many surgeons reserve the hypothermic bypass procedure for giant aneurysms or other complex aneurysms with wide or ill-defined necks in the posterior circulation. These aneurysms, despite the use of microsurgery and modern exposure techniques, remain daunting surgical challenges. The principal advantage of hypothermic arrest is to convert an otherwise inoperable aneurysm into one that has a reasonable chance of being clipped, while minimizing the risk of intraoperative catastrophe.

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Functional Mapping for Surgically Removing Brain Tumors

SURGICALLY REMOVING intrinsic brain tumors can reduce elevated intracranial pressure, improve neurologic function, stop recurrent seizures, and prolong quality survival. The goal of surgical intervention for intrinsic brain tumors should be maximal resection of tumor without producing new neurologic deficits. Despite advances such as the use of perioperative glucocorticoids and the operating microscope, there is still a substantial incidence of increased neurologic deficit—as high as 11% in some series—following attempted tumor resection. Intraoperative functional mapping of the cortex can increase the safety of the surgical removal of brain tumors and has become an accepted adjuvant to it.

The essential site for a given function is usually localized, but the location may vary among persons, especially for language. In some patients, vital functions have been found within the tumor. Operations based on standard anatomic landmarks do not take this variability into consideration.

Despite the myriad of simple and complex functions accomplished by the brain, only a few tests are required to increase the margin of safety when operating in

important cortical regions. The most commonly mapped functions include motor and sensory (simple functions) and language and memory (higher cortical functions).

Preoperative studies are done to help predict functional anatomy. Neuropsychometric studies can predict hemispheric dominance and document subtle preexisting cognitive deficits in areas such as verbal and visuospatial memory. The Wada test (intracarotid amobarbital administration during cerebral angiography) transiently disrupts function in one hemisphere, allowing the confirmation of hemispheric dominance. Newer modalities such as magnetic source imaging and functional magnetic resonance imaging promise to augment the armamentarium of noninvasive mapping, but have yet to replace conventional computed tomography or magnetic resonance imaging as standard preoperative studies.

During the surgical procedure, electrical stimulation mapping identifies functional cortex. When an electrical current is applied to the surface of the brain, a reversible localized depolarization elicits or blocks the function of that portion of the brain until the current is removed. Motor movements can be seen, sensory phenomena can be reported, and language can be interrupted during language tasks. Craniotomies while patients are awake are possible because the brain does not feel pain or touch. With a regional local anesthetic block and propofol, an ultrashort-acting intravenous anesthetic agent, patients are put to sleep for the opening without requiring intubation, awakened for the functional mapping, and put back to sleep for the remainder of the operation and the closure. Once awake, low currents and 60-Hz biphasic square wave pulses of 1-millisecond duration are used to map the motor and sensory cortices of the face and hand. In dominant-hemisphere operations, the patient is asked to count aloud, and stimulation mapping then identifies counting arrest sites. These sites are usually associated with face motor function. Language sites are mapped by applying the current to the brain surface while the patient names slides of simple objects every four to five seconds. Other modalities such as vision, the ability to read music, to generate verbs from nouns, to speak a second language, to perform sign language, and to do mathematical calculations can also be mapped if necessary. Once important functions are identified, the operation continues with the avoidance of functional areas. With these techniques, permanent neurologic morbidity from tumor resection operations can be kept below 5%.

Brain mapping techniques increase the safety of brain tumor operations and allow for tumor resection with less risk of postoperative deficit.

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Percutaneous Discectomy—Update

PERCUTANEOUS TECHNIQUES for treating radiculopathy due to herniated lumbar discs have stimulated keen interest. This interest is prompted by a need for less invasive techniques, experience with percutaneous approaches in other surgical specialties, and rapidly advancing technology.

The first procedures for percutaneous discectomy used fluoroscopically guided manual instruments that were designed to remove nucleus pulposus (nucleotomy) and possibly contiguous herniated fragments through an intradiscal approach. An automated disc aspirator and laser have recently been used to remove larger amounts of nuclear material in a shorter time. These procedures are purported to decrease irritation of the nerve root and other innervated structures by either eliminating inflammatory mediators (disc material) or reducing intradiscal pressure. Automated disc extraction has recently been found to remove minimal amounts of disc in a sheep model, leading investigators to hypothesize that perforation of the annulus alone may be responsible for the observed clinical results. Reported outcomes for both manual and automated nucleotomy range from 44% to 85%, with results lasting as long as two years, compared with 75% to 90% with routine microdiscectomy. Complications have been rare, but include infection, hemorrhage, damage to the lumbar nerve roots, penetration of instruments into the thecal sac, and injury to the cauda equina.

Newer technologies are making simple nucleotomy obsolete as surgeons now can remove disc fragments that are impinging on nerve roots and percutaneously fuse degenerated disc spaces. Stereotactic localization of intradiscal targets and disc fragments to avoid entry into the thecal sac or damage to extraspinal nerve roots and vessels is being investigated. Stereotactic localization may eventually be used to guide instruments directly to an offending disc fragment within the neural foramina, allowing its removal.

With an intradiscal approach, angled instruments and aspiration probes guided by both rigid and flexible endoscopes are being used in an attempt to remove the nuclear material in disc bulges and to snare free fragments. This technology is also being used to remove fragments through foraminal approaches because the endoscope allows the exiting nerve root, vessels, and herniated fragments in the foramina to be easily identified. With these technologies, the concept of removing large amounts of nucleus and concomitantly reducing intradiscal pressure may be moot as the offending herniation is able to be removed.

Along with newer instruments, various multiportal approaches are being attempted with endoscopes and specialized tools to better remove nuclear material and view and remove fragments accurately from an intradiscal approach. Disc spaces are also being fused using these approaches and a transabdominal approach. Whether these approaches are superior to a single-tract approach has yet to be determined.

The growing excitement for percutaneous techniques should be tempered by an honest assessment of the

success of these techniques. Although many articles have reported substantial short-term clinical improvement following a variety of different percutaneous techniques, a multicenter, prospective, randomized study comparing percutaneous discectomy with open lumbar microdiscectomy has not been done. The National Institutes of Health has recently funded such a study, to be undertaken at several centers throughout the United States. The results of this study will provide a base on which to assess further advances in percutaneous technology.

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Tethered Cord Syndrome

THE TETHERED CORD SYNDROME is an increasingly recognized clinical disorder usually associated with spinal defects such as myelomeningocele, diastematomyelia, lipomyelomeningocele, thickened filum terminale, and intradural lipoma. Tumors such as epidermoids or dermoids, arachnoiditis, and iatrogenic retethering from suturing can also be responsible for the syndrome.

A diagnosis of tethered spinal cord is made when symptoms occur because the conus medullaris is below the level of L-2. The pathophysiology, which has been delineated by many investigators, is that the spinal cord is subject to injury from mechanical, vascular, and metabolic forces when it is placed under tension from the aforementioned lesions.

The clinical picture can be dramatic or insidious. Both motor and sensory loss develop, or patients have a change in their bladder or bowel function. Young children will have skeletal growth deformities such as a leg-length discrepancy or scoliosis. Adolescent or young adult patients often complain of long-term back pain. Physical examination findings can be unimpressive or include a combination of lower and upper motoneuron abnormalities. Good clues to the presence of a tethered spinal cord are cutaneous signs associated with occult spinal dysraphism, such as an abnormal hair pattern in the lumbosacral area ("fawn tail"), fatty masses associated with lipomyelomeningocele or perhaps deep dimples or sinus tracts, or small angiomatous-appearing birthmarks in the midlumbar areas. Of course, the skeletal deformities can be found on examination.

Evaluation of such findings should include magnetic resonance imaging (MRI) of the lumbosacral spine. This standard imaging study will detect the presence of a tethered spinal cord and almost always will delineate the cause. Exceptions might be in cases of thickened filum terminale, which can be difficult to ascertain even on a high-quality MRI. In infants, a high-resolution ultrasound examination can often be a good screening test because the conus can be shown nicely and many of the lesions detected.

A patient's lower urinary tract should also be evaluated. Urodynamic studies are sensitive indicators of lower tract compromise. When available, this would be the preferred examination. Follow-up urodynamic studies will often be the first indicator of retethering effects, perhaps before the patient is aware of any changes in function and certainly before any changes in the neurologic system can be found.

Most American pediatric neurosurgeons recommend that patients with the tethered cord syndrome have exploration and release of the spinal cord at the time of diagnosis. This position is controversial and is not completely embraced by the European medical community. Nevertheless, there is good evidence that a preemptive release of a tethered spinal cord to prevent the occurrence of neurologic and urologic deficits is in a patient's best interest. Often function is not completely restored if the operation is done after a deficit has already occurred.

Operative techniques and requirements for special instrumentation vary depending on the specific disorder and a surgeon's experience. Lipomyelomeningoceles and diastematomyelias often present great challenges. Many find the operative microscope especially useful for visualization and minimal manipulation of neural tissue. A spacious dural closure is more important than a total resection of the intradural fatty elements in lipomyelomeningoceles. Procedures to remove dermal sinus tracts are the easiest, as the tract can be kept intact and followed through the fascial defect to its termination at the dura or beyond.

The issue of retethering after the initial operation has generated a great amount of attention. Various suggestions and techniques for minimizing the incidence of retethering have been put forth, but none have proved to be completely effective or superior. They range from simplistic maneuvering, such as placing gel film over the neural elements before dural closure, to the use of plastic and silastic interposition materials, to actually reconstituting the posterior neural arches with bone grafts.

A frequent concern is patients with myelomeningocele in whom spasticity has developed in the lower extremities or neurologic function is being lost. These patients represent the most difficult management issues because they have a high propensity to retether. At the initial repair of myelomeningoceles, a suture of the neural placode with fine, absorbable suture material to reconstitute a neural tube has been advocated to minimize the retethering possibilities.

Surgical management, although challenging, is usually rewarding. Patients with a painful tethered cord syndrome almost invariably have relief of pain following the procedure. Often patients who have incontinence become continent, and many of the children with

myelomeningocele who have regressed to wheelchairs can return to assisted ambulation.

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Managing Chronic Intractable Pain

NEUROSURGICAL PROCEDURES are often the last resort for patients suffering from chronic intractable pain. There are two types of neurosurgical procedures for this purpose: reversible procedures such as deep brain stimulators, spinal cord stimulators, and pump devices for prolonged delivery of medications to the spine and brain and irreversible ablative procedures, such as rhizotomies, cordotomies, tractotomies, thalamotomies, and dorsal root entry zone. Proper patient selection is crucial.

Fully implantable pumps are currently used mainly for delivering morphine sulfate or baclofen. As with all other opioids, tolerance can develop. The proper selection of patients and of the appropriate neurosurgical procedures improves results and cost-effectiveness. With better pain control, patients are likely to return to a more active life and decrease their use of ineffective alternative treatments. For both patient selection and treatment, a multidisciplinary team is needed that consists of a neurosurgeon, anesthesiologist, psychiatrist, nurse clinicians, and when dealing with cancer patients, an oncologist. The morphine pump is mainly used for some types of neuropathic pain and for somatic pain. Good to excellent results are reported in 80% of patients with cancer. In general, neuropathic pain such as burning, painful numbness, or painful dysesthesia responds better to neurostimulation or ablation.

Neurophysiologic pain mechanisms are complex and not well understood. To have a patient considered a candidate for a pump implantation, there should be evidence of disease, a failure of conservative treatment, analgesia induced by a preoperative trial, neuropsychological clearance, no morphine allergy, and an expected remaining life expectancy of more than three months. A complete neurologic workup is an absolute requirement.

Intrathecal narcotic infusion appears to act primarily in the spinal cord at the presynaptic and postsynaptic receptors in the substantia gelatinosa. The analgesia obtained does not interfere with tactile sensation, motor function, or sympathetic activity. In patients with chronic intractable pain, responses are quantified using the visual pain analogue system, in which 0 is no pain and 10 is the worst possible pain. Other measurements evaluate the patient's psychological state before surgical treatment, the patient's need for parenteral analgesics, and the patient's limitations due to pain.

The most commonly used pump is 6.3 cm (2½ in) in diameter, 2.5 cm (1 in) thick, and weighs 170 grams (6 oz). It has a reservoir and a microprocessor that is externally programmed, using telemetry, to infuse automatically. The pump is programmed according to a patient's analgesic requirements. It can also program a special "bolus" for periods of increased pain during the day. A programming error or inadequate surgical technique will result in complications. There is a built-in alarm in the pump that alerts the patient to a malfunction. The battery lasts three to five years. The catheter from the pump is inserted directly into the spinal canal or into the ventricular system of the brain. Patients with cancer pain who are taking parenteral narcotics frequently have to decide between drowsiness or pain. This can be avoided by using small doses of intrathecal medication. Intrathecal administration of morphine does not lead to addiction.

Surgical implantation can be done with the use of local or general anesthesia. With the help of a C-arm fluoroscope, the intraspinal catheter is inserted and then is fixed or anchored to the supraspinous ligament or fascia. An abdominal subcutaneous surgical pocket is made at a predetermined site, and the spinal catheter is connected to the abdominal pump subcutaneously.

The use of intrathecal baclofen has been found recently to decrease dysesthetic pain in some patients with spinal cord injury, transverse myelitis, multiple sclerosis, or spasm-related pain. About 70% of patients with spinal cord injuries and 45% of patients with multiple sclerosis have chronic pain, mainly of the dysesthetic type. The use of baclofen in infusion pumps reduces rigidity and decreases the incidence of muscle spasms. Baclofen binds presynaptic γ-aminobutyrate$_B$ receptors in the brain stem, dorsal horn of the cord, and other central nervous system sites. It has also been used in patients with cerebral palsy in whom spasticity abated, but the athetosis was unaffected. In patients with postherpetic neuralgia in whom the use of intrathecal morphine has failed, a therapeutic infusion trial with intrathecal baclofen can be effective.

Physicians, patients, and families generally lack understanding about chronic pain. It is common for patients to become suicidal when they cannot achieve pain relief and continue to suffer unrelenting pain. The goal of the morphine pump and other neurosurgical pain procedures is not to deal with the underlying disease but to control the pain symptoms.

Medicare has recently approved the use of intrathecal infusion pumps for the treatment of chronic pain due to both malignant and benign disease. Patients who do not respond to local central nervous system narcotic medications for pain control may yet benefit from this type of neurosurgical pain procedure.

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Dorsal Rhizotomy for Spasticity

IN UPPER MOTONEURON lesions of various types, spasticity is often a major cause of disability. In children with cerebral palsy, the spastic type is most prevalent and is becoming more common due to improved survival rates of premature infants with low birth weights who are susceptible to early central nervous system damage. Dorsal rhizotomy for the purpose of reducing spasticity was reported as early as 1908. The procedure has been revised over time to improve its safety and efficacy. It has been used for both adults and children with various diagnoses, but has been most widely and successfully employed for selected children with spastic cerebral palsy.

Spasticity is defined as a velocity-dependent resistance to stretch with a "clasp-knife" quality that is associated with hyperactive tendon reflexes and clonus. It is thought to be caused by a decrease in inhibitory influences at the level of the α-motoneuron due to damage to descending motor tracts. Cerebral palsy is a multifaceted motor disorder that varies in severity and extent of limb and body involvement. Features may include spasticity, dystonia, secondary contractures and deformities, impaired balance, persistent and exaggerated infantile reflexes, weakness, and disordered motor control. Some children with severe quadriplegia or total body involvement undergo the rhizotomy procedure with a goal of facilitating positioning, handling, and orthopedic care. The remaining candidates are ambulatory children with spastic diplegia who have pure spasticity without dystonia, display relatively good balance, strength, and motor control, and have limited preexisting contractures and bony deformities. These features are assessed clinically by a team that includes a neurosurgeon, physical therapist, and an orthopedic surgeon.

Spasticity should be a major factor in a child's physical disability if rhizotomy is being considered; structural changes such as bony torsion or fixed contractures must be addressed by an orthopedic specialist. During dorsal rhizotomy, a multilevel, narrow, midline laminotomy is used to provide access to the nerve rootlets of the cauda equina. Spasticity is diminished by selectively dividing sensory nerve rootlets associated with signs of hyperreactivity in response to electrical stimulation. A laminoplasty is done at the end of the procedure.

Outcome studies by several authors have shown reduced spasticity or resistance to passive range of motion and increased range of joint motion following rhizotomy. Functional improvements have been more difficult to quantify, but rating of gross motor skills has revealed improvements in developmental postures, transitional movements, and walking ability. Early studies reported improvements in range of motion at the hip and knee during gait that were associated with increased speed and stride length, and these were maintained at least three years after the operation. Greater ankle range of motion during gait has also been reported. Electromyographic studies showed a loss of clonic activity in response to quick muscle stretch. Increased energy efficiency during gait has been reported for ambulatory spastic children. Some studies have suggested dramatic postoperative improvement in coordination in children with spastic diplegia who had independent walking function before the operation.

Specific complications of this procedure, such as dural leakages, sensory or motor deficits, sphincter disturbances, and exacerbation or unmasking of notable muscle weakness, have been uncommon. Concerns have arisen regarding a possible increased predisposition to skeletal problems such as hip dislocation or spinal deformity in children. A review of more than 100 cases found no important surgical or early postsurgical complications in these patients. Follow-up of patients receiving multilevel laminectomies (rather than laminotomies) revealed the development of scoliosis and spondylolisthesis in a small percentage of patients, but these spinal deformities have been shown to develop in patients with cerebral palsy who have not undergone rhizotomy at an even higher rate. Progressive hip subluxation following rhizotomy may occur in children with preexisting hip dysplasia, but existing hip deformities generally either abate or progress no further after surgical reduction of spasticity.

Selective posterior rhizotomy for reducing spasticity is an effective procedure that is beneficial for certain patients with spastic cerebral palsy. For a successful outcome, a multidisciplinary team approach to the management of cerebral palsy is required, along with careful and conservative selection of appropriate surgical candidates. During the operation it is important to meet the goal of reducing spasticity while sparing as many nerve rootlets as possible. Preoperative and postoperative therapy with an emphasis on functional strengthening is thought to be essential for optimal benefit from the alteration in muscle tone. Orthopedic management is needed in concert with the neurosurgical procedure to address existing structural deformities and to prevent future musculoskeletal problems. Further systematic evaluation of the neurophysiology of spasticity and the clinical features of children with cerebral palsy should improve future patient assessment and management.

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Stabilizing the Cervical Spine

THE GOALS OF MANAGING patients with an unstable cervical spine are to prevent further neurologic injury, provide an optimal environment for neurologic recovery, and ensure a long-term, stable, pain-free spine. Correcting malalignment, immobilizing, and administering methylprednisolone sodium succinate if there is an acute spinal cord injury are the key factors to prevent further neurologic injury and provide the best environment for neurologic recovery. The use of very-high-dose methylprednisolone represents a major advance in the treatment of patients with spinal cord injury: methylprednisolone therapy improves motor and sensory return in patients with incomplete or complete spinal cord injury, but only if administered within eight hours of the injury.

The healing of damaged bone and soft tissue to provide a long-term, stable, pain-free spinal column requires immobilization by surgical or nonoperative means. Nonoperative techniques rely on external devices, such as the Halo vest, cervicothoracic brace, and Philadelphia collar. The Halo vest provides the most rigidity and the Philadelphia collar the least. Advances in surgical techniques permit rigid internal fixation of the cervical spine from either anterior or posterior approaches, reducing or eliminating the need for orthoses such as the Halo vest. Anterior techniques use titanium plates affixed to the vertebral bodies with screws. Posterior techniques include interspinous wire fixation, interlaminar clamps, or titanium plates affixed by screws inserted into the lateral mass of the cervical spine. The purpose of all these implant systems is to hold the spine in a rigid position while bone fusion occurs. All of the systems will eventually fail unless bone healing occurs. Therefore, surgical implants serve only as temporary splints.

These implants add substantially to the cost of an operation, with prices of plates varying from $150 to $1,000 and those of individual screws ranging from $15 to $75 each. Given the cost of these systems, what are the indications for using them? Implants are clearly indicated in certain kinds of cervical spine trauma, based on a classification of cervical spine stability developed by White and Panjabi. Bilateral jumped-facet injuries or burst fractures with substantial injury to the posterior ligamentous structures are likely to heal poorly if only an external orthosis is used; therefore, surgical intervention is likely to provide benefit. Less clear are indications for internal fixation and stabilization of degenerative spine disease. Unlike in trauma, ligamentous structures are likely to be intact and degenerative joint disease leads to reduced mobility of the cervical spine as a whole, making instability after surgical intervention less likely. Single-level fusion rates exceed 90%, making implants an unnecessary adjunct to good surgical technique. Implants can improve rates of fusion after bone grafting in multilevel anterior discectomy and fusion.

Metastatic disease to the cervical spine often weakens bone and ligaments, provoking spine instability with accompanying pain and possible neurologic compromise. Surgical intervention alone typically further destabilizes, making internal fixation devices important in these cases, especially as many of the patients are metabolically depleted because of disease or therapy. Implants provide important stability while bone and soft tissues heal.

Internal fixation devices in the cervical spine have reduced the need for cumbersome external orthoses, like the Halo device. Caution should be exercised by physicians in determining which patients are most likely to benefit from internal fixation. Anterior plate fixation devices (Morscher system, Caspar system) have been approved by the Food and Drug Administration (FDA) for implementation in the spine. The posterior, lateral mass plates are FDA-approved, but not specifically for use in the spine. Although the morbidity and mortality of surgical implantation are relatively low, sound judgment and experience will prevent the inappropriate use of these devices. Bone and ligamentous structures are most likely to be affected by trauma or metastatic disease and are therefore the most likely to demonstrate instability.

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Neuroendoscopy

THE FIRST NEUROENDOSCOPIC PROCEDURE was carried out 84 years ago. Recently there has been a renewed interest in neuroendoscopy and its role in the management of intracranial tumors, hydrocephalus, intracranial hematomas, neuroanatomic subarachnoid cistern navigation, and the management of lumbar disc protrusions.

The role of intracranial neuroendoscopy in the management of intracranial tumors is limited. Biopsy can certainly be done under direct vision for tumors within the ventricle. Specimens are small, however, which makes the tissue difficult to analyze. Tumors particularly amenable to an endoscopic approach are those in the lateral and third ventricles and those of the pineal region. The difficulties encountered with stereotactic approaches through the brain parenchyma, crossing pial surfaces blindly, are reduced with an intraventricular route. Colloid cysts of the third ventricle can also be aspirated and their walls coagulated using contact potassium-titanyl-phosphate or neodymium-yttrium-aluminum-garnet lasers. A direct visual approach with endoscopy reduces the risk of vascular injury at the foramen of Monro, which was sometimes reported with closed stereotactic approaches. Endoscopy may also have a role in the fenestration of tumor cysts that occur within the brain parenchyma and to allow for the communication of cysts with one another and with the ventricular system. Intraventricular cysts that are seen in children can also be

fenestrated under direct vision with contact lasers or monopolar instruments.

The accurate placement of ventriculoperitoneal shunts from an occipital route can also now be assured using 1.2-mm rigid scopes that pass down the center of the shunt catheter. In this way, the catheter can be placed under direct vision into the frontal horn of the lateral ventricle away from the choroid plexus, possibly reducing the chances of future obstruction. Entrapped shunt catheter tips in choroid plexuses can also now be removed, again under direct vision with contact lasers, reducing the risks of hemorrhage with catheter removal. Third ventriculostomy can also be performed in patients with noncommunicating or obstructive hydrocephalus, when an obstruction exists between the posterior third ventricle and the outflow through the foramen of Magendie, avoiding the need for a permanent shunt. The procedure is not without complications, however, and cases of hemorrhage from small perforated vessels in the interpeduncular subarachnoid space, bradycardia, and a case of cardiac arrest, as well as postoperative transient diabetes insipidus and the syndrome of inappropriate antidiuretic hormone, have occurred with this procedure.

The use of endoscopes for evacuating intracranial hematomas has received little attention in North American circles. The aim is to reduce intracranial pressure by removing most, but not all, of a blood clot with the endoscope. Further evaluation with prospective clinical trials is needed.

Other possible applications of intracranial neuroendoscopy include navigation of the subarachnoid cisterns, particularly in the region of saccular intracranial aneurysms. With small curved endoscopes, the posterior aspect of the neck of an aneurysm can be observed, and in real time, during clip application, the position of the distal aneurysm clip can be observed relative to the aneurysm neck and parent vessel. This may help with the accurate first-time placement of an aneurysm clip that completely occludes the aneurysm neck. In a similar way, for skull-base tumors adjacent to large major vessels, the relationship of the tumor to these vessels can be discerned with small flexible and rigid endoscopes at either end of the tumor. Combining rigid endoscopes with frameless stereotactic devices gives the added information of real-time magnetic resonance imaging (MRI) or computed tomographic two-dimensional imaging positions of the endoscopic tip at the same time as the operator views directly through the endoscope. This is particularly helpful where normal anatomical landmarks are missing, such as within a tumor cyst, hematoma cavity, or a multiloculated porencephalic area.

Spinal neuroendoscopy to date has rarely been used as a therapeutic tool. A recent report of a prospective, randomized study comparing the technique with that of standard lumbar microdiscectomy found equally good, if not superior, results with percutaneous endoscopic methods. During standard open operations, small-angled endoscopes can be used to examine the nerve root foramen for persistent or sequestered disc fragments. The efficacy of endoscopic techniques in the surgical management of lumbar disc protrusions requires further evaluation.

Future applications of neuroendoscopy will likely include other combinations with real-time interactive image-guided surgery using frameless stereotactic devices, magnetic field localization, and real-time MRI. As with any other technology, rigorous review and follow-up of clinical cases and their subsequent report in peer-reviewed journals will determine the usefulness of these techniques.

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Role of Spinal Instrumentation in Fusion for Degenerative Disease of the Lumbosacral Spine

It has been estimated that 50% to 70% of the population will have at least one episode of back pain associated with the lumbar spine. In fact, 14% of new-patient visits to physicians are attributed to lower back pain. About 4% of the population will undergo a lumbar spine operation in their lifetime. The Bureau of National Health Data Statistics states that problems of the lumbar spine cost about $16 billion a year for surgical therapy, continued treatment, and time lost from work. Spinal fusion techniques have been an important management strategy for traumatic conditions of the lumbar spine and less frequently for various degenerative conditions. Adding internal fixation and instrumentation devices during arthrodesis allows the correction of a deformity that might not have been feasible otherwise. In addition, instrumentation minimizes motion during graft incorporation and thereby increases the rate of solid arthrodesis, especially over several anatomic motion segments.

Specific indications for spinal fusions are supported by reports in the literature and clinical experience, such as stability and correction or prevention of deformity. Adding instrumentation as an adjunct to the bony fixation ideally achieves the following: immediate stabilization of the spine, protection of neurologic function, correction of deformity associated with symptoms, earlier rehabilitation and hospital discharge, and less dependence on orthotics.

The rates of successful spinal fusion with bone graft alone can range from 46% to almost 100%. Because of increasing difficulties in achieving fusion and maintaining alignment of the spine, the popularity of spinal instrumentation has increased. In the lumbosacral spine, the

earlier techniques of spinous-process wiring, spinous-process plating, and sublaminar wires or hooks with rods that were useful in treating deformities appear to be less successful than the newer technique of using pedicular screws to correct degenerative conditions, especially when the posterior elements are not available for fixation.

The rate of fusion in patients with and without instrumentation is being examined. From these studies, it appears that rigid pedicular screw and rod fixation leads to a much higher percentage of fusions in degenerative lumbar disease than does fusion without instrumentation. The fusion rate also is higher with rigid instrumentation than with semirigid plate and screw fixation, although clinical results improved with both fixation systems. It also appears that the rate of pseudarthrosis is markedly decreased in patients receiving instrumentation compared with those receiving posterolateral fusions alone.

In conclusion, the treatment of each patient must be individually tailored. If fusion is indicated for certain symptomatic patients with degenerative lumbosacral spine disease who have instability or a deformity, then the fusion may be enhanced by instrumentation.

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Carotid Endarterectomy

THE EFFICACY OF CAROTID ENDARTERECTOMY in reducing the risk of stroke in patients with severe carotid stenosis (70% to 99%) and ipsilateral ischemic symptoms was demonstrated in 1991 with the reports of three randomized, prospective studies—the North American Symptomatic Carotid Endarterectomy Trial, the European Carotid Surgery Trial, and the Veterans Affairs Symptomatic Carotid Stenosis Trial No. 309. At that time, clinical trials to evaluate the benefit of endarterectomy in patients with asymptomatic carotid artery stenosis were ongoing. Recently the investigators of the Asymptomatic Carotid Atherosclerosis Study (ACAS) reported interim results that show that carotid endarterectomy, when combined with aggressive medical therapy, provides a substantially reduced risk of ipsilateral stroke in asymptomatic patients with greater than 60% stenosis compared with medical management and the use of aspirin alone.

The ACAS study was a randomized, prospective trial to assess whether carotid endarterectomy reduces the overall five-year risk of ipsilateral stroke. More than 1,600 patients were enrolled. The investigators observed the patients for any incidence of early stroke or death (within the perioperative or early postrandomization period) and any subsequent ipsilateral stroke. Carotid endarterectomy reduced the risk of stroke from nearly 11% to just under 5%, a relative risk reduction of 55% over medical treatment alone. The relative risk reduction was higher for men (69%) than for women (16%). Because statistical significance favoring carotid endarterectomy was reached, enrollment in the study was closed and the participating physicians were advised to reevaluate those patients randomly assigned to the nonsurgical group.

Together these studies support the general recommendation that patients with severe carotid stenosis of greater than 60% caused by atherosclerosis should undergo carotid endarterectomy. Low perioperative morbidity and mortality are imperative. The American Heart Association Stroke Council guidelines for acceptable limits on these rates vary with the indication for surgical intervention—3% for asymptomatic stenosis, 5% for transient ischemic attacks, 7% for previous stroke, and 10% for recurrent carotid stenosis. It is important to recognize that the studies had strict inclusion and exclusion criteria and that the appropriateness of surgical therapy ultimately depends on the medical condition of the patient. For example, the ACAS investigation excluded patients with unstable angina, uncontrolled atrial fibrillation or hypertension, severe diabetes mellitus, renal insufficiency, hepatic disease, and other conditions that made the risk of an operation unacceptably high. It should also be noted that all patients undergoing carotid endarterectomy in this study had preoperative arteriography and that surgical decision making on the basis of noninvasive studies alone was not addressed.

An estimated 500,000 new cases of cerebral infarction occur every year in the United States. It now appears that, in addition to medical therapy with aspirin and aggressive risk factor modification, carotid endarterectomy is emerging as an important adjunct in the management of carotid occlusive disease in well-defined patient groups. The benefit of endarterectomy for patients with less severe stenosis awaits further investigation, and the indications for the operation will continue to be refined.

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Alerts, Notices, and Case Reports

California's Public Health Policy on Preventing Neural Tube Defects by Folate Supplementation

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NEURAL TUBE DEFECTS, which include spina bifida and anencephaly, are among the most common, serious, and costly congenital malformations. About 4 anencephalic and 5 spina bifida births occur per 10,000 births in California. Mortality for anencephaly is almost 100% within the neonatal period. For spina bifida, about a third die in the neonatal period and more than 65% have serious handicaps. The Centers for Disease Control and Prevention (CDC) has estimated lifetime costs at $250,000 per survivor, which calculates as more than $62 million to care for the approximately 250 annual survivors of one California birth cohort.[1]

The CDC has issued a recommendation, based on its review of the literature, that all women at risk of pregnancy receive a daily folate supplement of 0.4 mg.[2] The California Department of Health Services has recently reviewed the available information, and in this alert makes its recommendations.

The evidence that folate can play a role in prevention, although indirect and based on small numbers, is convincing.[3-10] The results reported to date are summarized in Table 1. The various studies evaluating the effects of folate use are difficult to compare.[11,12] Some investigators studied groups that consisted of high-risk mothers of affected children who have a "recurrence" risk estimated at 2% to 5%. Others studied women with no previously affected children who have a lower first "occurrence" risk (0.09% in California).

The studies were also done in groups with different genetic and environmental characteristics because prevalence ranged from 0.09 to 6.0 cases of neural tube defect per 1,000 total births, that is, live births plus fetal deaths.[13-15]

The various studies used different definitions of supplementation based on the time it was started and the length of time it was taken: women took supplements for a varying number of weeks before conception, and supplementation continued for days to months after conception. Studies also varied in the amount of folate ingested daily; some actually studied dietary folate without supplementation. Other epidemiologic differences are also difficult to explain, such as the apparent racial differences in folate effectiveness reported by Mulinare and co-workers.[3]

Most of these studies of occurrence are retrospective and are subject to selection and recall bias. A prospective study done in Hungary reported that 0.8 mg of folate daily could prevent the occurrence of a substantial portion of cases of neural tube defects if given before and during early pregnancy.[9] The data in Hungary, which has a birth prevalence of neural tube defect about three times that in California, were based on a relatively small number of observations.

The best evidence for the prevention of recurrence was the randomized, double-blind, prospective, multicenter placebo study conducted by the Medical Research Council in England.[16] This study conclusively established that about 70% of cases of the expected recurrence could be prevented by 4.0 mg of folate daily taken from the date of entry to the study until 12 weeks after the last menstrual period. This study was done in countries with high prevalence. Based on this study and CDC recommendations,[17] the Department of Health Services advised physicians in California to encourage all women who had a fetus or infant affected or who had a close relative who has had an infant with neural tube defect to take 4.0 mg of folate daily before and during subsequent pregnancies. We have recently modified this recommendation in light of the more recent CDC publication to 0.4 mg a day interconceptionally and 4.0 mg a day periconceptionally.[2]

The cumulative weight of the evidence is that folate supplementation will prevent some cases of neural tube defects from occurring. In California, this could range from 20% to 50%. Therefore, the department endorses the goal of women of childbearing age taking at least 0.4 mg of folate daily. Women who have had a previous affected pregnancy or who have a history of neural tube defect in a close relative should have the level raised to 4.0 mg of folate daily whenever they are attempting to conceive. There is good reason to think that a lower dose, such as 1 mg daily, might be equally effective because studies show that much of the larger dose is lost in the urine.[18] This proposal has not been clinically verified, although there have been reports that taking a daily dose of 0.36 mg of folate substantially reduced recurrence rates.[19,20]

In arriving at this recommendation, we considered those variables that could influence the effectiveness of the folate prevention strategy. The first consideration is whether there is a critical time period for the ingestion of folate relative to the pregnancy. The neural tube forms

(Cunningham GC: California's public health policy on preventing neural tube defects by folate supplementation. West J Med 1995; 162:265-267)

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
FDA = Food and Drug Administration

from the 17th to 19th day after conception and closes by the 28th to the 30th day. When dated by the last menstrual period, closure is complete by a gestational age of about 42 to 44 days or 6.2 weeks. Analysis of folate metabolism indicates that the best measure of adequate folate intake is normal erythrocytic folate because folate stores are built up in the erythrocytes and liver. The serum folate level is only a measure of recent ingestion and can be normal even in a person with depleted folate stores. Only one study reported protection when supplemental folate was given after a positive pregnancy test or missed period.[6] It therefore appears that folate must be given in advance of pregnancy, taken daily, and continued at least for the first six weeks after the last menstrual period.

The next question, the minimum amount of folate needed to ensure protection, is also not clear, but most investigators use 0.4 mg or more per day. This would appear to be a safe dose, but because the metabolic mechanisms involved, including differential absorption, are unknown, some women may need larger amounts. There may be some difference in the bioavailability of dietary folate and supplemental folate tablets.

The department, having endorsed this preventive measure, reviewed the methods of implementation. The possibilities were as follows:

- A program of public education promoting a diet containing sufficient folate;
- The promotion of a folate supplement to be taken by women of childbearing age; and
- Dietary supplementation of cereals or other foods with folate.

The department concluded that dietary fortification was the most effective public health approach and communicated this position to the Food and Drug Administration (FDA).

After some initial misgivings, the FDA has proposed regulation that will permit the use of health claims—that is, prevention of neural tube defect—for foods and vitamin supplements containing sufficient folate and that will require the supplementation of grains and cereal staples with additional folate.[21,22] The department is concerned, however, that the levels of food fortification that the FDA is recommending for folate may be too low to appreciably affect the prevalence of neural tube defect.

In addition to any fortification undertaken, a program of public education as to the importance of adequate folate in the diet should be initiated to ensure that foods naturally high in folate or supplemented with folate will be consumed by women. The department's Women, Infants and Children's Supplemental Food Branch and Maternal and Child Health Branch will be responding to this need. The use of folate tablets or multivitamins containing 0.4 mg of folate should be encouraged if dietary intake is poor. The CDC reports that fewer than 30% of women have 0.4 mg or more of folate in their diets. Folate and folate-containing multivitamins are available on the Medi-Cal formulary. It is important that public education include a caution to women not to attempt to increase folate intake by ingesting excessive vitamin supplements, especially multivitamins. These may contain harmful concentrations of the fat-soluble vitamins, A and D.

We would like to caution against unreasonably high expectations, because defects occur even in women taking supplements. The reduction in birth prevalence of neural tube defect will probably be different from one group to another. The epidemiology and cause for areas of high prevalence are different from those with low prevalence.[23] There is a social gradient in risk and prevalence seen in several countries, but not in some low-prevalence areas. Birth prevalence has declined in areas of high prevalence, but has shown little change in areas of low prevalence. Therefore, the East Coast might have a notable decline in birth prevalence whereas California might well have only a modest decline of 10% to 20%.

Consideration must also be given to the possible adverse consequences of folate supplementation on some women, especially at the 4-mg dose recommended to prevent recurrences. The FDA reviewed this problem

TABLE 1.—*Reported Risk Reduction in Neural Tube Defect (NTD) Occurrence With Folates*

Study	Risk Reduction			Cases of NTD, No.	Controls, No.	Folate Type
	Minimum, %	Average, %	Maximum, %			
Mulinare et al, 1988[3]	34	59	74	347	2,829	Multivitamin supplement
Bower and Stanley, 1989[4]	+21	59	86	77	154	Dietary folate
Mills et al, 1989[5]	+20	0	17	571	573	Multivitamin supplement
Milunsky et al, 1989[6]	17	64	85	49	22,715	Multivitamin supplement
Bower and Stanley, 1992[7]	+109	0	49	23	36	Multivitamin supplement
Martínez-Frías and Rodríguez-Pinilla, 1992[8]	6	31	49	263	7,274	Multivitamin supplement
Czeizel and Dudás, 1992[9]	--	100	--	6	4,704	Multivitamin supplement
Werler et al, 1993[10]	20	60	80	436	3,672	Multivitamin supplement
Total				1,772	41,957	

and conservatively recommended that daily ingestion of folate be kept at 1 mg or less. Some have claimed that folate in sufficiently high dosage, such as 4 mg, can mitigate the effectiveness of some anticonvulsant medication, but there is little evidence to support the concern that a dosage of 0.4 mg daily will have this effect. Patients on valproate therapy need folate supplementation. The possibility should be considered that the megaloblastic anemia resulting from vitamin B_{12} deficiency could be corrected by supplemental folate therapy, whereas progressive neurologic deterioration would not be prevented in the absence of parenteral or oral vitamin B_{12} therapy. This form of anemia is rare in women of childbearing age. It appears, however, that the folate supplementation levels recommended for preventing occurrence, 0.4 mg a day, are unlikely to contribute substantially to this problem. It is not justified to expose pregnancies to the risk of neural tube defect to achieve early diagnosis of this anemia. The risks of higher doses of folate recommended to prevent recurrence must be weighed against the 2% to 5% recurrence risk.

Because in all these studies cases of neural tube defect occur even in women with high levels of folate, pregnant women need to be given the opportunity to be screened, using the California Maternal Serum α-Fetoprotein screening program. In addition, such screening will find abdominal wall defects and cases of Down syndrome that would otherwise go undetected.

Many questions remain unanswered with respect to the relationship of folate to neural tube defects. What is the lowest effective dose? What is the difference between folate-sensitive and folate-resistant cases? Is there an effect on all forms of neural tube defect, such as high defects—above the level of the 12th thoracic vertebra—versus low defects; isolated neural tube defect versus neural tube defect with additional malformations; open versus closed lesions, encephalocele, and the like? Are other nutrients, such as vitamin B_{12}, zinc, or vitamin C, involved in enhancing or inhibiting the preventive effects of folate?

In view of the unanswered questions about what fraction of cases are preventable in California, it is important to the public and clinicians that the department collect data on the occurrence of cases subsequent to folate fortification of foods and widespread folate supplementation. In California, there is mandatory reporting of all cases of neural tube defect diagnosed before 1 year of age. The department collects additional reports from maternal serum α-fetoprotein screening, prenatal diagnostic centers, hospitals, hospital discharge summaries, and fetal and live birth certificates to supplement reporting. The number of cases diagnosed by ultrasonography and terminated without reporting through one of these data collection systems is unknown, however. We encourage all physicians to report these unreported cases, as required by law, to improve the reliability of our evaluating the neural tube defect prevention program. Reporting forms are available on request by calling the Genetic Disease Branch at (510) 540-2534.

The department will continue to monitor this situation and the effectiveness of all prevention efforts as part of its broader goal to prevent birth defects and to improve pregnancy results for all women in California.

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Sustained Atrial Fibrillation After Dobutamine Stress Echocardiography in an Older Patient With Left Atrial Enlargement

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STRESS ECHOCARDIOGRAPHY is a relatively new and valuable diagnostic tool.[1] The use of dobutamine as a pharmacologic stressor in conjunction with echocardiography is now fairly common as an aid in the diagnosis of coronary artery disease.[2] I present a case of newly occurring sustained atrial fibrillation after dobutamine stress echocardiographic evaluation that failed to convert to sinus rhythm.

Report of a Case

The patient, a 73-year-old man with morbid obesity, was seen because of progressive dyspnea for a year. In 1989 the patient underwent a standard treadmill evaluation that was a submaximal test because of low exercise tolerance. At that time, there was no chest pain or electrocardiographic (ECG) changes suggestive of ischemia. He also reported that over the previous year he would have several episodes of paroxysmal nocturnal dyspnea per week. He did not have orthopnea, pedal edema, chest pain, or cough. He had no history of cardiopulmonary disease.

The patient was a past smoker (40 pack-years) but quit eight years ago. He denied any other risk factors for cardiopulmonary disease. There was no occupational exposure or recent known exposure to lung irritants. He has had obstructive sleep apnea, which was successfully treated with nocturnal nasal continuous positive airway pressure. His weight has been stable over the past five years. The patient's only medication is terazosin hydrochloride, 2 mg orally at bedtime, for symptoms of bladder outlet obstruction.

On physical examination the patient appeared in no acute distress. He was normotensive, and no abnormalities were detected on the physical examination. The initial laboratory evaluation elicited normal values on pulmonary function tests, arterial blood gas measurements with the patient breathing room air, thyroid function tests, complete blood count, multichannel chemistry panel, and urinalysis. A chest x-ray film was remarkable for old scarring at the right base, unchanged from previous films. A 12-lead ECG demonstrated normal sinus rhythm with left atrial enlargement. Normal sinus rhythm was also seen on previous ECGs.

Because of the possibility that his exertional dyspnea represented an anginal equivalent and in view of the patient's poor exercise tolerance, a dobutamine stress echocardiogram was obtained. The resting images showed normal left ventricular function with no appreciable valvular abnormalities. Left atrial enlargement was documented at 4.5 cm. During dobutamine infusion, the patient's contractility was normal. He had a normotensive response to dobutamine infusion, and no ischemic wall motion abnormalities were detected. At an infusion rate of 50 μg per kg per minute, the patient went into atrial fibrillation with a ventricular response in the 80s. He was asymptomatic with this.

He was seen again in the clinic three weeks later, and a follow-up ECG demonstrated atrial fibrillation. A regimen of warfarin sodium (Coumadin) was started, and the patient was seen four weeks later for an elective electrocardioversion. Cardioversion was attempted, but despite using as much as 300 J, the patient remained in atrial fibrillation.

Discussion

Nonsustained atrial fibrillation has previously been reported with the use of dobutamine stress echocardiography.[3-10] This is the first reported case of atrial fibrillation, presumably induced by dobutamine stress echocardiography, that did not spontaneously or electrically convert to normal sinus rhythm. A case has previously been reported of a patient maintaining an undefined supraventricular rhythm for three hours after undergoing dobutamine stress echocardiography; conversion to sinus rhythm was eventually attained, however.[10] In the largest series of patients who underwent dobutamine electrocardiography (n = 1,118), 7 cases of atrial fibrillation occurred.[7] All of these patients converted spontaneously or with the administration of digoxin. In the next largest series, 8 cases of nonsustained atrial fibrillation were documented in 626 patients undergoing dobutamine stress echocardiography. A history of ventricular arrhythmias and resting wall-motion abnormalities was associated with an increased risk of dobutamine-induced dysrhythmia.[8]

In a report comparing dobutamine stress echocardiography, dipyridamole stress echocardiography, and standard exercise stress testing, 80 patients received as much as 40 μg per kg per minute of dobutamine.[4] In this series, a supraventricular arrhythmia developed in 6 patients (8%). None of the supraventricular arrhythmias were sustained.[4] In another study, 136 patients were assessed by dobutamine stress echocardiography before having vascular operations. Doses as high as 40 μg per kg per minute were used, and one episode of paroxysmal atrial fibrillation occurred that converted to normal sinus rhythm with the administration of metoprolol tartrate.[3]

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In a series of 74 male patients, one episode of nonsustained atrial fibrillation also occurred with the use of doses of dobutamine as high as 40 μg per kg per minute.[9]

Several investigators have reported small series of dobutamine stress echocardiography with no episodes of atrial fibrillation.[11-15] In an analysis of 61 patients undergoing dobutamine stress echocardiography, no episodes of atrial fibrillation occurred.[11] In fact, premature atrial and ventricular contractions were mentioned as the only deviation from sinus rhythm, despite using doses as high as 50 μg per kg per minute.[11] In another series, 50 patients were studied using "low-dose" dobutamine (as much as 20 μg per kg per minute), and 4 episodes of vagally mediated hypotension with slow junctional rhythm and 1 episode of nonsustained supraventricular tachycardia were documented. In addition, 5 patients had premature atrial contractions, and 10 patients had premature ventricular contractions.[12] In another report, no malignant arrhythmias occurred with a similar "low-dose" dobutamine (as much as 30 μg per kg per minute) protocol.[15] Our patient went into atrial fibrillation at a dose of 50 μg per kg per minute, and although low-dose dobutamine stress echocardiography may be less arrhythmogenic,[12,15] many authors think that doses of as high as 40 to 50 μg per kg per minute are necessary to obtain maximum yield in detecting coronary artery disease.[4,6,7]

The only report specifically addressing dobutamine stress echocardiography in older patients is an analysis of 63 patients older than 60 years. In this report, 5 patients had either nonsustained supraventricular tachycardia or premature ventricular contractions. The rate of arrhythmias in older and younger patients was not substantially different, indicating that age alone is not a predictor of increased risk for dobutamine-induced arrhythmias.[5]

Alternatives to dobutamine as a pharmacologic stressor in stress echocardiography have been investigated.[4,13,16] One group showed dobutamine to be more sensitive in detecting coronary artery disease, but failed to show a significant difference in accuracy between dobutamine, dipyridamole, and adenosine as adjuncts in stress echocardiography.[13] In an analysis of 57 patients with known coronary artery disease undergoing stress echocardiography, the authors observed dobutamine to be more sensitive in patients with single-vessel disease, but failed to detect a significant difference between dobutamine and dipyridamole in patients with multivessel disease. Adverse events in each group were uncommon, but the incidence of arrhythmias was considerably less in the group given dipyridamole.[4] A significant difference in sensitivity was not found between dobutamine and dipyridamole in patients on antianginal therapy at the time of their stress echocardiogram.[16]

Dobutamine causes atrial fibrillation by enhanced atrial automaticity while decreasing the refractory period of accessory atrial pacemaker cells.[17] In concert with this is our patient's low-dose α-blocker use, which perhaps enhanced the β_1 effect of dobutamine. Also present is underlying conduction system disease, as evidenced by the slow ventricular response observed at the onset of atrial fibrillation, which may, in combination with the above, contribute to the pathogenesis of our patient's atrial fibrillation.

The failure of conversion to sinus rhythm makes this case unique. Although the patient's left atrium was mildly enlarged, left ventricular function was normal during rest imaging, and no ischemic changes were seen with dobutamine infusion. One has to postulate that in rare patients, dobutamine may irreversibly affect atrial impulse formation, leading to atrial fibrillation. Cardioversion was not attempted sooner because of the misguided notion that arrhythmias observed with dobutamine stress echocardiography are self-limiting. The patient was not started on antiarrhythmic therapy because of the failure during cardioversion to enter sinus rhythm.

Dobutamine stress echocardiography is a useful noninvasive test of coronary perfusion. Although its use should not change, perhaps patients at risk for atrial fibrillation—such as those with left atrial enlargement or a history of atrial fibrillation or valvular heart disease—should be considered for an alternative pharmacologic stressor such as dipyridamole or adenosine.

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Rhabdomyolysis From Tourniquet Trauma in a Patient With Hypothyroidism

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RHABDOMYOLYSIS is a syndrome produced by an acute skeletal muscle insult, resulting in the release of large amounts of intracellular muscle contents.[1] The diagnosis is suggested by a pronounced elevation of creatine kinase (CK) levels and pigmenturia with the absence of erythrocytes (myoglobinuria). Rhabdomyolysis may result in acute renal failure, multiple organ system failure, and death. The most common underlying causes are trauma, intense physical exertion, excessive alcohol intake, and seizures.[1] Hypothyroidism and intraoperative tourniquet trauma are rare causes of rhabdomyolysis.[2,3] We report the case of a patient with hypothyroidism and intraoperative tourniquet application in whom rhabdomyolysis developed.

Report of a Case

The patient, a 30-year-old man with hypothyroidism, was transferred from another military medical facility for the management of postoperative rhabdomyolysis. He had hypothyroidism for four years following an episode of Hashimoto's thyroiditis, and required a daily replacement dosage of 350 μg of levothyroxine sodium. Two weeks before an elective operation, he discontinued this medication and failed to reveal his history of hypothyroidism during the preoperative evaluation. The day before admission to the San Diego, California, Naval Medical Center, the patient underwent a left anterior cruciate ligament reconstruction and meniscus repair under epidural anesthesia. A thigh tourniquet was applied intraoperatively for 131 minutes at 300 mm of mercury. After the procedure, the patient complained of continued "numbness" of his left leg despite normal findings on a neurovascular examination. He was given one dose of intramuscular ketorolac tromethamine for pain relief. About 18 hours after the operation, the patient had severe thigh pain and dark urine. Urinalysis at that time revealed a specific gravity of 1.025 and a pH of 5.5; dipstick showed a 4+ reaction to blood; microscopy showed 1 to 4 erythrocytes and 5 to 9 leukocytes per high-power field. A urine salt precipitation test was positive for myoglobin.[4]

Other laboratory tests were done and revealed a normal complete blood count, coagulation panel, and electrolytes. An initial CK level was greater than 50,000 U per liter (normal, 0 to 265); aspartate aminotransferase, 1,411 U per liter (normal, 0 to 41); alanine aminotransferase, 307 U per liter (normal, 0 to 40); lactate dehydrogenase, 997 U per liter (normal, 100 to 225); albumin, 31 grams per liter (3.1 grams per dl) (normal, 34 to 54); and creatinine 97 μmol per liter (1.1 mg per dl) (normal, 44 to 141).

A diagnosis of rhabdomyolysis was made. A regimen of forced diuresis using a normal saline solution and urinary alkalinization was instituted. The patient did well, maintaining good urinary output (>150 ml per hour), with rapid clearing of the myoglobinuria and a decline in serum CK levels. The lower extremity swelling, pain, and hypoesthesia slowly resolved. No notable increase in his blood urea nitrogen or creatinine concentration occurred. Thyroid function tests on admission revealed a serum thyroxine level of 23 nmol per liter (1.8 μg per dl) (normal, 63 to 138) and a thyroid-stimulating hormone level of 56 mIU per ml (normal, 0.38 to 6.1).

Discussion

Anesthesia and surgery in patients with hypothyroidism may lead to a number of complications. In a study of hypothyroid patients undergoing surgical therapy, it was shown that an increased incidence of intraoperative hypotension, perioperative heart failure, gastrointestinal hypomotility, and neuropsychiatric disease occurred.[5] Muscle abnormalities including elevated CK levels, myalgias, and weakness are common in patients with hypothyroidism.[6] Rhabdomyolysis is rarely precipitated by hypothyroidism alone,[2] but hypothyroidism may interact with other factors (such as medications) to precipitate rhabdomyolysis.[7] Rhabdomyolysis has not been reported as a complication of surgery in hypothyroid patients.

Tourniquets are widely used for both orthopedic and podiatric operations, with infrequent complications. "Safe" tourniquet time is influenced by many factors, including general health, age, presence of peripheral vascular disease, and the amount of reversible tissue damage that is acceptable.[8] The optimal tourniquet time and pressure are unknown, but because muscle injury is a direct effect of tourniquet pressure, the minimal amount of pressure required to maintain a bloodless field is used. For normotensive patients with compliant vessels, pressures of greater than 300 to 350 mm of mercury are rarely required.[9] Tourniquet times of less than an hour appear to be the safest in preventing muscle and nerve injury,[10] although studies suggest that minimal tissue injury occurs with as long as 180 minutes of ischemia, provided there is a 5-minute midapplication

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release time.[8] Rhabdomyolysis after tourniquet usage is rare, but it can be precipitated by prolonged tourniquet compression.[3]

Rhabdomyolysis appears to have developed in our patient from the combined effects of hypothyroidism and tourniquet application. Classic clinical components of rhabdomyolysis, including edema, severe pain, and muscle weakness, were present before the development of myoglobinuria.[1] Clinicians need to be aware of the possible causes of rhabdomyolysis—including hypothyroidism and tourniquet application—and the importance of prompt treatment to prevent progression to renal failure. Rhabdomyolysis should be included as a possible complication of surgical therapy in hypothyroid patients, and thyroid function tests should be an integral part of the preoperative assessment for patients with known or suspected hypothyroidism.

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Editorials

Screening for Prostate Cancer Today

In 1993 the American Cancer Society recommended that the routine yearly physical examination for all men older than 50 years should include digital examination of the prostate and obtaining a blood specimen for determining the prostate-specific antigen (PSA) level.[1] The American Urological Association officially concurs with this recommendation. In practice today, a substantial proportion of physicians involved in the primary care of adult men are routinely obtaining a serum PSA measurement to supplement their examination of the prostate, and based on the results of these examinations, a large and growing number of men are being referred to specialists for additional evaluation and testing, commonly including transrectal ultrasound imaging of the prostate and biopsies. Thus, in the United States today, relatively aggressive screening for prostate cancer is already a common and widespread practice. Perhaps it is then a moot point to debate and investigate this practice. I hope not.

Cher and Carroll elsewhere in this journal provide a timely and insightful review of much of the background information that currently exists pertaining to screening men for prostate cancer.[2] Certainly, the sensitivity of the serum marker PSA to even small-volume prostate cancers has driven much of the present enthusiasm over screening. Serum PSA is a nonspecific marker for prostatic disease, and its measurement is for many reasons a less-than-perfect screening test, but it inarguably improves greatly our ability to detect prostate cancer in asymptomatic men, including those with no palpable abnormality on digital examination. Although the digital rectal examination is relatively insensitive compared with the PSA assay, it is simple, nonmorbid, and inexpensive, has a separate role in screening for gastrointestinal cancer, and does detect some prostate cancers that the PSA test does not. Together, obtaining a blood specimen for a PSA test and doing a digital prostate examination are easily accomplished at relatively low cost, have been shown to have significant sensitivity and positive predictive value for screening, and, with a cutoff PSA level of 4.0 ng per ml with the most common Hybritech PSA assay, they will detect most prostate cancers while still organ confined and potentially curable.[3] Hence, if screening is to be done, the existing evidence supports the use of the PSA test and digital examination as our best and most practical means to detect prostate cancer today.

Cher and Carroll have correctly concluded that transrectal ultrasound examination of the prostate is not a good screening test for prostate cancer.[2] Ultrasonographic findings are neither sufficiently sensitive nor specific, and the examination is invasive, time-consuming, and costly. In an asymptomatic man electing to undergo prostate cancer screening and having abnormalities found on a prostate examination or PSA assay, biopsy is indicated regardless of ultrasonographic findings. Transrectal ultrasonography is routinely used to facilitate biopsy of the prostate and increases the accuracy, yield, and range of biopsy—not only enabling guided-needle biopsy of specific hypoechoic lesions, but together with the currently used spring-loaded biopsy guns, allowing controlled systematic sampling throughout the prostatic peripheral zone, biopsy of the anterior and nonpalpable transition zone of the prostate, and even biopsy of the seminal vesicles and extraprostatic tissues, if indicated.

Although we may be able to identify the best tools available to screen for prostate cancer, many other questions related to screening for this malignant disease remain more resistant to easy answer. It is important for every physician and patient involved in the process of screening for prostate cancer to be cognizant of some of these limitations in our present knowledge base. For instance, the optimal threshold PSA value for biopsy is not exactly defined. Whereas a cutoff value of 4.0 ng per ml using the Hybritech assay is widely supported, both lower and higher cutoff levels are suggested by some data.[3-6] The optimal threshold may depend on a patient's age and prostate size (the concept of PSA density), to name just two possible confounding factors.

Although the common recommendation is to begin screening at the age of 50, certain subpopulations, including African Americans and men with a notable family history of prostate cancer, might optimally begin routine screening at an earlier age, with 40 years arbitrarily suggested by some physicians. No recommendation is offered by the American Cancer Society or American Urological Association for a maximum screening age, but it certainly makes good medical and economic sense that we should not be subjecting asymptomatic 80-year-old men to routine PSA assays. Should the cutoff for routine screening be 75 or 70 years of age, or younger? A practical rule of thumb that many follow is to require a minimum estimated life expectancy of at least 10 to 15 years to justify screening an asymptomatic man for prostate cancer. In practice, however, this can be difficult to judge, especially for a specialist physician meeting a patient for the first time. General internists or family practitioners providing primary care, with knowledge of an individual patient accumulated over time, may be best equipped to judge life expectancy, and these physicians can and must provide important insight—and exercise restraint—regarding the value of prostate cancer screening for any individual man.

Although current recommendations are for serial, yearly screening to detect prostate cancer, data so far indicate that most cancers are found in the first year of screening, with diminishing returns thereafter.[7] Most likely, a man with a normal PSA level and digital prostate examination at age 50 can be safely and more

economically observed with serial examinations at two- or three-year intervals or greater, based on our knowledge of the progression of small, early prostate cancers, but no study has yet addressed this aspect of screening.[8] Similarly, formal recommendations are lacking for men presenting with an elevated PSA level or abnormalities on a digital examination, but biopsies that fail to show cancer. How often should these examinations and invasive biopsies be repeated before we can be satisfied that a serious cancer is adequately excluded? Again, we have no scientific data on which to base an answer, and many patients are faced with exactly this conundrum while being subjected to multiple procedures over an extended period of time because an elevated serum PSA level cannot otherwise be explained.

Fortunately, initial fears regarding the sensitivity of PSA screening resulting in the identification of an excessive number of small, clinically unimportant prostate cancers that will never cause morbidity have apparently not been realized, although a few patients with such cancers are now being subjected to aggressive and morbid therapy to attain cure where none is really needed. Most accept this as a regrettable but inevitable by-product of successful screening, so long as the number of such patients remains small. Of more general concern and interest is whether finding prostate cancers earlier by screening must necessitate immediate treatment. Curative therapy is morbid, and long-term problems with sexual potency and urinary continence are not uncommon. Can an early cancer found in the sixth decade by screening be safely observed and still subjected to cure in the seventh decade, so as to prevent morbidity and mortality from prostate cancer in the eighth decade, and at the same time delaying any morbidity related to therapy for many years? Work that better defines the natural history of prostate cancer and identifies the prognosis for individual lesions in individual patients may eventually allow us to determine which asymptomatic cancers detected by screening can be safely observed for extended periods and which are truly unimportant and will never require therapy.[8,9] Such information might substantially minimize the very real possible morbidity of mass screening programs and may provide one of the final and determining components in the ultimate argument to justify prostate cancer screening for all men. Such data do not currently exist.

Meanwhile, prostate cancer remains far and away the most common nonskin cancer in American men, with an incidence that is more than double that for lung cancer and that is greater than the combined incidence for lung and colorectal cancer in this population (the second and third most common nonskin cancers, respectively, in United States men).[10] The American Cancer Society estimates that 244,000 new cases of prostate cancer will be diagnosed in the United States in 1995 and that more than 40,000 men in this country will die of prostate cancer over the course of the year—110 every day.

Given numbers of this magnitude, it is understandable—perhaps even justifiable—that the public and their concerned physicians should react and that this reaction should include requests and proposals to actively screen men for prostate cancer in the hope that earlier detection might improve survival from this disease. In some respects, this reaction is as much visceral as cerebral. When the details of prostate cancer screening are examined carefully and scientifically, it is recognized that many important questions are still unanswered, and it remains an undeniable fact that no scientific study to date has demonstrated the ability of screening to reduce mortality from prostate cancer. This has led some to reject, on a strictly scientific basis, the concept of screening our population for this disease, and careful future studies may yet prove these persons correct.[11,12] At present, however, such a stance has become increasingly difficult to defend against the available investigational data, the overwhelming epidemiologic numbers, the public concern and the desire for screening and intervention, and our own human concern to do everything in our power as physicians to lessen the effects of this disease. If we feel it is best to screen men for prostate cancer today—and as physicians and human beings we must at times do what we "feel" is best when our science cannot yet provide every answer—then let us at least proceed as rationally as possible, based on those facts we do know.

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Total Hip Arthroplasty—A Cure?

MORE THAN 30 years have passed since the late Sir John Charnley ushered in the modern era of prosthetic total hip replacement with his "low-friction" arthroplasty operation.[1] This rather glamorous name obscures the fact that despite its recognized success in treating disabling hip disease, total hip arthroplasty is in reality an internal amputation. Hip replacement is an operative procedure that involves an internal resection of the hip joint with prosthetic replacement. This solution to the difficult problem of hip arthritis has brought tremendous relief to patients, but hardly constitutes a cure.

The interest of most orthopedic surgeons performing this operation has been with perfecting their surgical technique and the technology of the procedure.[2] Major areas of investigation for these prosthetic devices have been biocompatibility, material strength, reproducing joint mechanics, prosthetic fixation to bone, and wear of the weight-bearing surfaces. Dramatic progress has been achieved in several technical areas. The prostheses are generally well tolerated by the adjacent tissues, seldom break, and allow near-normal hip function for ordinary daily activities. Long-term biocompatibility and bone remodeling around these devices are still under investigation. Attaching these prostheses to the adjacent bone in a permanent manner remains a problem, and the promise of biologic fixation without acrylic cement is still evolving. Wear of the bearing surfaces is a major problem that threatens the longevity of these devices. The particulate wear debris from the articulating surfaces can lead to bone destruction and loosening of the prosthesis. Ceramic bearing surfaces may be the best choice in terms of wear performance, but concerns exist about their strength.

In this issue of the journal, Siopack and Jergesen present a complete and objective overview of total hip arthroplasty.[3] They describe the procedure, materials, and surgical indications. The problems and early and late complications are also addressed. Despite the limitations of total hip arthroplasty, the overall effectiveness in terms of patient satisfaction and outcome is well established. Millions of patients with disabling hip disease have had hip function restored following total hip arthroplasty, allowing them to walk, sit, and sleep without pain. Other surgical alternatives such as osteotomy to realign the joint surfaces or arthrodesis, where the joint is fused, remain as viable options in selected patients, especially younger ones.

Further research may solve the technical problems that remain with these prosthetic devices, but there are those who argue that we are reaching the limits of what can be achieved with current materials and technology. Total hip replacement is currently an effective operation, but the future for the treatment of patients with disabling arthritis may lie elsewhere.

Articular cartilage is at the center of the arthritis problem. This smooth glistening tissue that covers the ends of our long bones to form synovial joints is the site of arthritic interference with joint function. Osteoarthritis is the most common form of arthritis that afflicts patients, usually as they get older. It leads to progressive deterioration of articular cartilage that eventually results in exposed bone surfaces articulating against each other, producing joint stiffness and pain, the clinical hallmark of arthritis.

To approach this disease from a biologic perspective will require a method of restoring or maintaining the structure of living articular cartilage.[4] The properties of this unique tissue cannot be duplicated by any known metal or plastic device. Much ongoing research is devoted to biologic methods of restoring articular surfaces. Some of the more interesting approaches involve using tissue transplants such as periosteal and perichondral grafts or the implantation of chondrocytes or mesenchymal stem cells to generate new tissue.[5] Isolating chondrogenic biochemical factors that could be delivered to the joint at an early stage of the disease would be ideal. The day when we can inject a substance into the joint that will arrest the progression of the disease or, better yet, restore the integrity of damaged articular cartilage, is still far off.

For at least the next decade, however, prosthetic replacement of arthritic hip joints will likely remain the most effective surgical option for advanced disabling osteoarthritis of the hip in elderly patients.

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Radiologic Case

Intracavitary Mass in a Patient With Tuberculous Pneumonia

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 62-year-old woman with insulin-dependent diabetes mellitus was admitted to the hospital with fever, cough, and night sweats of three weeks' duration. She was febrile (38.3°C [101°F]), and chest auscultation revealed bronchial breath sounds over the right upper lung. A sputum examination showed acid-fast bacilli, and a sputum culture grew Mycobacterium tuberculosis. *A chest roentgenogram (Figure 1) revealed right upper lobe consolidation. Therapy for tuberculosis was instituted one day after admission, with the patient responding well. A second chest roentgenogram (Figure 2) and a computed tomographic (CT) scan of the chest (Figure 3) were done ten days later.*

What are the findings?

What do they represent?

What is the prognosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A posteroanterior chest roentgenogram shows right upper lobe consolidation.

Figure 2.—A second posteroanterior chest roentgenogram was taken 10 days after the first.

(Annamaneni A, Padmanabhan K: Intracavitary mass in a patient with tuberculous pneumonia. West J Med 1995; 162:275-276)

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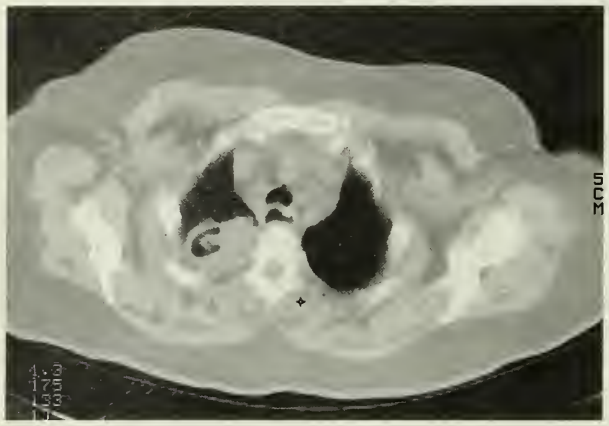

Figure 3.—A computed tomographic scan of the chest shows the right upper lobe.

ANSWER:

Pulmonary gangrene due to pulmonary tuberculosis

THE SECOND CHEST FILM (Figure 2) shows substantial resolution of the right upper lobe consolidation. A cavity with an intracavitary mass is now seen in the right upper lobe, both on the chest roentgenogram (Figure 2) and the CT scan of the chest (Figure 3). This rapid progression from consolidation to cavitation with an intracavitary mass is the characteristic radiographic finding of pulmonary gangrene.[1] An early radiographic sign—called the crescent sign—is the development of a rim of air within the consolidated lung.[2]

Inflammatory necrosis of lung tissue occurs as a result of pyogenic, tuberculous, and fungal infections. Ischemic necrosis and gangrene of lung tissue are the result of localized arteritis, thrombosis, and vascular compression from the inflammatory exudate at the site of lung infection. As the devitalized lung parenchyma demarcates from the viable lung tissue, a rim of air within the area of consolidation may be seen on the chest film (crescent sign).[2] When this devitalized lung tissue sloughs off and settles on the floor of the cavity, an intracavitary mass is seen on the chest film. Various terms have been used to describe the same disease,[1] including massive sequestration of lung, gangrene with spontaneous amputation, spontaneous lobectomy, infarction of a pulmonary lobe, massive necrosis of lung, and massive pulmonary gangrene.

Pulmonary gangrene resulting from lung infection is uncommon. Only 33 well-documented cases have been described. The responsible pathogens include *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Aspergillus* species, and species of the order Mucorales.[1-6] When tuberculosis leads to pulmonary gangrene, the radiographic finding on presentation has invariably been one of consolidation, rather than the more characteristic radiographic appearance of pulmonary tuberculosis—that is, upper lobe infiltrates with cavities.

The development of pulmonary gangrene carries a grave prognosis irrespective of the causative organism. Of the 33 patients, 9 (27%) died as a result of the lung infection. Of the 24 patients who survived, 16 (67%) required surgical resection of the gangrenous lung tissue. When pulmonary gangrene develops in a patient being treated for pneumonia, resection of the diseased lung tissue by lobectomy or pneumonectomy is indicated if the clinical response is inadequate. Early and appropriate antibiotic therapy may obviate the need for surgical intervention and still ensure a successful outcome.

Recognizing gangrene of the lung is important because this complication has both therapeutic and prognostic implications. Making this diagnosis requires a familiarity with the characteristic radiographic appearance.

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Correspondence

Ocular Infections

To the Editor: In his editorial in the December 1994 issue, Whitcher misquotes our paper.[1] Dr Whitcher indicates that 48.1% of corneal ulcers cared for by a tertiary care corneal and external disease service do not have cultures performed. This is incorrect. In our paper, we reported on the practices within the Southern California community.[2] We reported that 48.1% of patients with corneal ulcers referred to our institution had been placed on antibiotic therapy before the referral, without cultures having been taken. In a survey of general ophthalmologists, we learned that 48.7% of corneal ulcers were similarly treated without cultures. In describing our own practice, we state, "We performed complete microbiologic examination of all ulcers at the time of initial examination at our institution. We teach our resident staff to do the same and include such teaching in our continuing medical education program." Thus, Dr Whitcher's editorial misstates our approach to this problem. In fact, although empirical antibiotic therapy for suspected microbial keratitis is common in the community, we are not aware of any cornea and external diseases specialists who do not routinely perform microbiologic workup of such lesions.

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* * *

Dr Whitcher Responds

To the Editor: After reviewing the article by McDonnell and colleagues, I find that they are correct in their criticism of my editorial. I misquoted their conclusions, and I concur with the content of their letter.

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Intravenous Immune Globulin

To the Editor: High-dose intravenous immune globulin (IGIV) is used with frequency to treat a wide range of immune-mediated diseases including immune hematologic disorders, systemic lupus, polymyositis, and dermatomyositis.[1-5]

Dalakas and colleagues stated that "high-dose intravenous immune globulin is a safe and effective treatment for refractory dermatomyositis,"[6(p1993)] although they described "severe headache with each infusion" in two of eight patients so treated. While the possible benefit of IGIV therapy outweighs the risk of adverse effects, the occurrence of aseptic meningitis following IGIV infusion is a complication that must not be overlooked.

Report of a Case

The patient, a 46-year-old man, had fatigue, generalized myalgia, arthralgia, low-grade fever, patchy muscle tenderness, and progressive, severe, bilateral calf and hamstring muscle pain develop in June 1985. The patient had an elevated sedimentation rate of 42 to 50 mm per hour and hypercholesterolemia, but no other abnormality. No underlying malignant disorder was found. Polymyositis was confirmed by electromyogram and electromicroscopy of muscle biopsy specimens. Progressive disease with myocardial involvement developed, and high-dose steroid therapy achieved only temporary improvement. Treatment with azathioprine (Imuran) led to partial remission, but had to be discontinued because of severe pancreatitis. Treatment with IGIV (1 gram per kilogram per day for 2 days) was started on November 4, 1991, because of progressive muscle weakness leading to total disability. Severe headache, intractable vomiting, fever, neck stiffness, lethargy, and a positive Kernig's sign developed 48 hours later. Analysis of the cerebrospinal fluid showed pleocytosis, but normal results for protein, glucose, and other studies. All cultures were negative.

Aseptic meningitis was diagnosed, and supportive treatment was given, along with low-dose methylprednisolone sodium succinate. Full neurologic recovery required a two-week hospital stay. A remarkable but transitory improvement of muscle strength and decrease in myalgia was noted, but no further IGIV was given. It is likely that acute aseptic meningitis was a complication of the intravenous infusion of immune globulin in this patient. A report was submitted to the Food and Drug Administration.

Recurrent migraine of unclear mechanism has been reported after the administration of high-dose IGIV.[7] Aseptic meningitis was reported following immune globulin therapy for immune thrombocytopenia.[9,10] Our case indicates that acute aseptic meningitis may complicate the use of IGIV in collagen vascular diseases. Although this complication occurs relatively infrequently, physicians should be aware of this potentially serious side effect.

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Rural Physicians—In Crisis?

To the Editor: More and more, primary care physicians (generalists, and perhaps family physicians most of all) are being recognized as cost-effective instruments for providing health care services. The problem we have as a profession is that:

- We do not know how to select medical students who will make good generalists.
- We do not make a serious attempt to train or support the training of good generalists—a term that many subspecialists seem to think is an oxymoron.
- We do not pay generalists very well—and we seem to think that is appropriate.

Rural health care is entering a time of crisis. Primary care physicians in rural areas are experiencing a reduction in reimbursement under fee-for-service programs. Managed care has not penetrated to most rural areas. Primary care physicians are in demand in urban areas, and their pay scale is rising. The consequences of this economic misfit is that the poor will become poorer—physicians will find that dedication will not sustain them in rural practices and will leave for the easier life and better pay of urban practice. What will rural residents do for health care services?

There are many of us who are willing to practice, even at modest financial disadvantage, in a rural setting. The economic disincentives are increasingly reaching the threshold for action. We will need to be supported financially if our profession is to avert a crisis that will deprive us of the control of our own destinies in rural California.

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Correction

In Hamlin and Kahn's article in the January issue[1] Figure 3 on page 28 was printed upside down. The correct figure is shown below. This was our error, and we apologize to Drs Hamlin and Kahn.

Figure 3.—A 39-year-old man who had previously undergone repair of bilateral complex inguinal hernias presented with groin pain bilaterally. The physical examination showed no abnormalities on the right and was equivocal for a hernia on the left. The herniogram showed a recurrent indirect inguinal hernia on the left (angled view) and no recurrence on the right.

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Lessons From the Practice

Confessions of a Closet Paternalist

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The pastor was just beginning to read the scripture when an usher tapped me on the shoulder and whispered that there was an emergency in the rear of the church. As I was directed through the door of the pastor's study, I encountered a scene of semiorderly panic: one person was calling 911; another was bursting through a door on the opposite side of the room shouting, "I know CPR, can I help?" and another was wringing her hands as she stood beside a motionless form lying on her back in the middle of the floor.

I knelt beside a well-dressed elderly woman who was pale, apneic, pulseless, and had a sizeable healing abrasion on her right forehead. My calm professional exterior belied the internal panic I felt at being thrust into a medical emergency with no stethoscope, blood pressure cuff, cardiac monitor, or equipment to measure blood gases. As I began going through the "ABCs" [airway, breathing, circulation], I found that the way she was positioned had caused the tight collar of her red silk blouse to constrict her throat. When I loosened two buttons, she gasped and started slow but unlabored, spontaneous breathing. Within moments there was also a weak and rapid pulse.

On direct questioning, the woman wringing her hands, Mrs McCarthy, reported that this was Mrs Pulaski, aged 93, to whom she gave a ride to church each Sunday. She was under the care of a physician and was on five or six medicines for diabetes, high blood pressure, and a heart condition and was also on a new medicine for "nerves." She lived alone and was quite independent. She had mentioned that morning that she had fallen at home the previous Monday—an explanation for the healing wound on her forehead. She had suddenly slumped over in church without warning, now three or four minutes ago. As this history was gathered, the unconscious woman began to stir. She first mumbled something unintelligible, and Mrs McCarthy recognized that Mrs Pulaski was coming around in Polish. As the four paramedics arrived with several pieces of equipment, she was switching to heavily accented English and was saying she felt fine and wanted to go home.

The paramedics moved in to administer oxygen, check her blood pressure, and apply the cardiac monitor and pulse oximeter. They carefully explained to Mrs Pulaski each intervention as it was applied, and she increasingly resisted each one. While the emergency medical technicians did their job very professionally, I began my differential diagnosis: simple syncope, hypoglycemia, oversedation or drug interaction from her new "nerve" medicine, subdural hematoma causing a seizure, or an arrhythmia that also could have caused the earlier fall. She needed to go to the emergency department at the hospital just six blocks away for further evaluation.

The technician in charge said to Mrs Pulaski, "We would like to put you on the stretcher and take you to the hospital to see your doctor. Is that OK?" I bit my tongue as I thought, Hasn't he been listening? "Is that OK"! Of course it's not going to be OK. She has already said six times that she wants to go home.

An unbalanced conversation ensued. The paramedic was calm and quiet and was trying to explain the need for further evaluation. Mrs Pulaski was loud and irate, not hearing anything he was saying and demanding that she be taken home. She even tried to blame poor Mrs McCarthy with, "This wouldn't have happened if you hadn't brought me to church!" This was going nowhere fast. It was then that my closet door opened, and I heard this authoritative voice from within me say to the paramedic in a tone reserved for wayward children, "Don't ask her permission. Just put her on the stretcher and take her to the ER."

The reason that voice both frightened and surprised me is that I teach clinical ethics to medical students and residents. I emphasize a patient's right to self-determination. I decry paternalistic behavior by physicians—behavior that we say was common in the past, but is much less common today. But here it was alive and well within my professional being. Could I salvage this situation from catastrophe?

I knelt again by her side and said rather firmly, "Mrs Pulaski, it is not normal to fall at home and injure yourself and then to pass out again in church a few days later. Something is wrong. It may be some problem with your medication, or it may be something more serious that needs to be fixed in the hospital. But we don't know now. We are going to take you to the Emergency

(Orr RD: Confessions of a closet paternalist. West J Med 1995; 162:279-280)

From the Department of Family Medicine, Loma Linda University School of Medicine, Loma Linda, California.
Reprint requests to Robert D. Orr, MD, 11340 Mountain View Ave, Bridgeport-C, Loma Linda, CA 92354.

Department at the hospital and call your doctor to come and sort out the problem. Now we are ready to help you onto the stretcher. Put your hand on my shoulder." She mumbled in Polish, but she put her hand on my shoulder. The ambulance left forthwith.

Rather than return to the middle of the sanctuary to sit with my wife, I took Mrs Pulaski's now-vacant seat in the rear pew. I heard nothing of the sermon. I tried to muster a defense for this paternalistic stranger who lived in my closet. I give a lecture to residents on "Patient Refusal of Physicians' Recommendations." *Patients have a right to self-determination, a right even extending to the refusal of potentially life-sustaining interventions.* Mrs Pulaski's situation was probably not life threatening. The crisis had passed spontaneously, and she was stable within a few minutes. *We must be sure the patient is competent to make decisions, has been adequately informed of the consequences of refusal, and is not being coerced; persuasion is OK, but manipulation and coercion are not.* She appeared to be competent. The emergency technician was trying to give her adequate information, though rather unsuccessfully. The utterance from the stranger in my closet certainly sounded coercive. *There are narrowly defined circumstances when paternalism may be justified. When a competent patient is making a seriously irrational choice that is not consistent with her chosen therapeutic goals and the harm done by overriding her choice is less than the harm done by acceding, it may rarely be ethically permissible to ignore her choice.* Mrs Pulaski's situation did not fit that description. Then what went wrong?

I immediately recalled a Franz Ingelfinger essay in which he says, ". . . the physician should recommend a specific course of action" and "[a] physician who merely spreads an array of vendibles in front of the patient and then says 'Go ahead and choose, it's your life' is guilty of shirking his duty, if not malpractice" (F. J. Ingelfinger: "Arrogance," *The New England Journal of Medicine*, 1980, 303:1507-1511). The utterance in question was born of frustration from watching another medical professional who was being too objective and not being sufficiently "arrogant" in this beneficent sense; one who was failing in his responsibility to give strong professional guidance in a serious situation.

As the pastor pronounced the benediction, I was trying to determine whether the closet door had been opened from the outside or the inside.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Continued from Page 213)

April 12-14—**Family Practice Refresher Course.** University of Utah Department of Family and Preventive Medicine at Salt Lake Hilton Hotel. Wed-Fri. Contact: UUSM.

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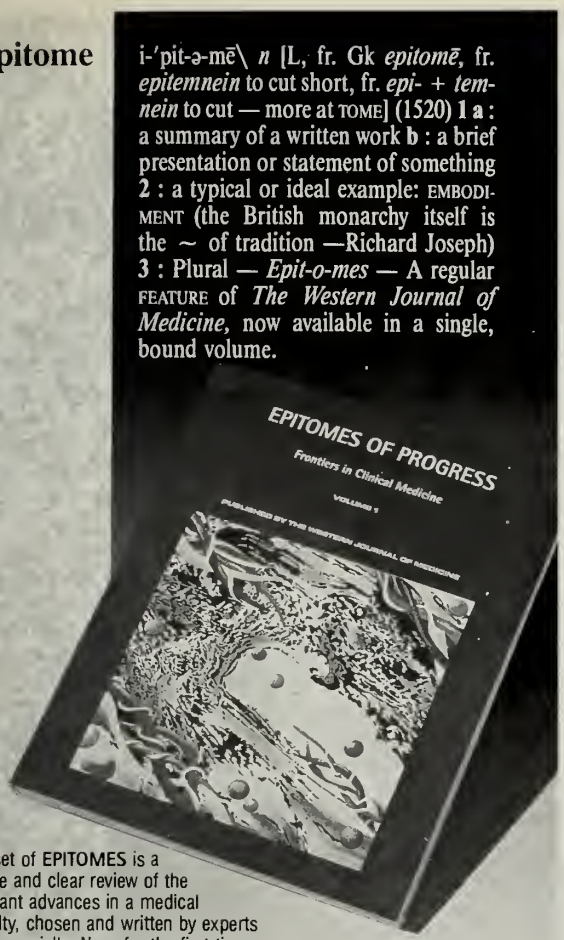

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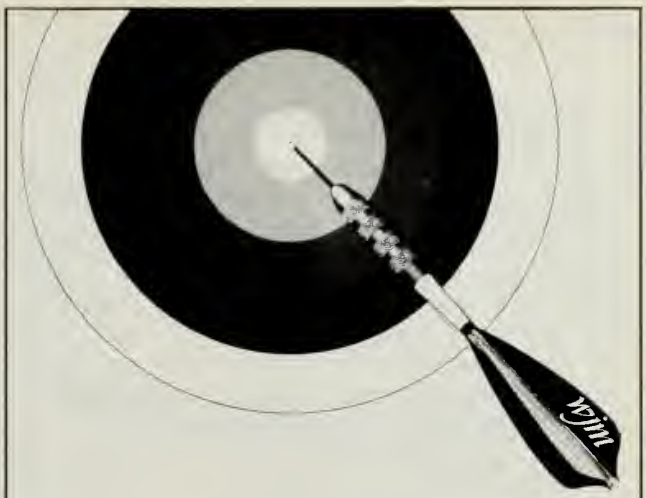

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Hal Werner, MD,
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Venture East

Primary Care Physicians and Subspecialists are being sought for a variety of group practices located throughout the upper Midwest and New York State. Choose from metropolitan cities, college towns, popular resort communities, or traditional rural destinations. This month, opportunities available for physicians specializing in Family Practice, Internal Medicine, Pediatrics, Occupational Medicine, Hematology/Oncology, and Nephrology. New opportunities monthly! For all of the facts, call (800) 243-4353 or write to:

STRELCHECK AND ASSOCIATES, INC.,
10624 N PORT WASHINGTON RD,
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WESTERN STATES' OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services,
4975 E Butler, #133, Fresno, CA 93727.
Call (800) 873-0786. FAX (209) 252-3085

OREGON/WASHINGTON. BC/BE Family Physicians to join well-established, single specialty groups near Portland and Seattle. Generous guarantee, benefits, and partnership. Congenial colleagues, abundant recreational and cultural activities. OB optional. Jan, (800) 718-8868, (206) 718-8800. (No J-1 opps available.)

FAMILY PRACTITIONERS - CALIFORNIA. Two opportunities for BC/BE Family Practitioners at locations close to Fresno and in Lompoc. Outpatient clinic setting with weekday hours. No call, weekends, or holidays. Excellent remuneration and occurrence malpractice offered. Contact Ev Walters, (800) 288-8044, or FAX CV to (719) 598-7945.

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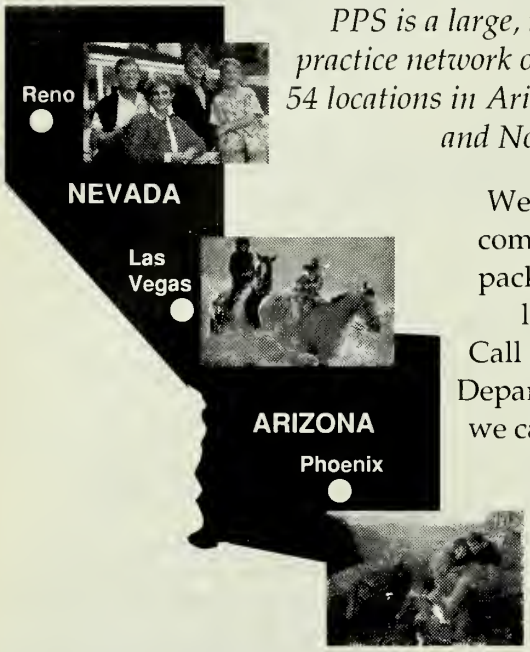
(PPS) is expanding in the Reno, Las Vegas and Phoenix areas and has opportunities for Family Practice & Urgent Care Specialists



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(PACIFIC NORTHWEST)

Pacific Northwest - Northwest Permanente, P.C., a physician-managed multispecialty group, has two full-time opportunities available for Board Certified/Eligible occupational medicine physicians, or other relevant primary care trained physicians, at our medical offices in Longview /Kelso, Washington.

Kaiser Permanente's Occupational Health Program in the Northwest Region (Oregon/Washington) has a total of 18 physicians and covers outpatient clinics at seven sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees.

We offer a competitive salary and benefits package which includes two comprehensive pension plans, paid professional liability, sabbatical leave and more. Please forward CV to: **W.J. Weiland, M.D., Regional Medical Director, Northwest Permanente, 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099.** EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.

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HCR

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Salary or Income Guarantee Opportunities

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ORTHOPAEDIST–BC/BE, California-licensed, needed for San Francisco-based multispecialty medical practice. Primarily forensic medical practice (evaluation and expert witness evaluations in workers' compensation, personal injury, etc). Excellent opportunity for experienced clinician looking to emphasize evaluation and consultation practice as opposed to heavy treatment-based practice. Full-time and part-time employment available, exceptionally high income potential, full benefits, and 401K. Submit CV and letter stating professional goals and availability to Administrator, 2040 Polk St, Box 337, San Francisco, CA 94109.

PHYSICIANS WANTED

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BC OR RECENTLY BE PHYSICIANS NEEDED. Los Angeles and Seattle metropolitan areas, WA, OR, AZ: Family Practice, Pediatrics, OB/GYN, and Urgent Care. Call Chris Warner, Panther Enterprises Physician Recruiting and Placement, (800) 235-7601.

FAMILY PRACTICE PHYSICIAN - NORTHERN CALIFORNIA. Full-time position in Native American ambulatory care clinic. Located in rural area with easy access to major metropolitan areas. Offers a multitude of recreation activities. Position salaried with excellent benefits. Monday-Friday, no evening/weekend call. Contact Diane Sevenau, Northern Valley Indian Health, Inc, 414 North Plumas Street, Willows, CA 95988, (916) 934-9293. EOE. Open until filled.

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Call Pat Lam, (800) 258-4526, 10-10 PST.

CALIFORNIA—Emergency Medicine/Family Practice. California Emergency Physicians Medical Group is a partnership of Emergency Medicine and ambulatory care specialists contracting with over 30 Emergency Departments and 10 ambulatory care centers in Northern, Central, and Southern California. We are seeking BC/BP Emergency Medicine and Family Practice Physicians. We offer attractive compensation, ownership, health, disability, and retirement benefits. Send your CV or contact John Gravette, CEP, 2101 Webster Street, Suite 1050, Oakland, CA 94612; (800) 842-2619.

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INTERNAL MEDICINE. Northern California. Expanding group practice in resort area. Two hours from San Francisco, one hour from ocean. Salary/benefits/coverage. Call Karlman Associates, (800) 634-3561.

PHYSICIANS WANTED

PRIMARY CARE

OREGON & S.W. WASHINGTON

Northwest Permanente, P.C., a professional group of physicians providing medical services to 380,000 members of Kaiser Permanente in Oregon and Southwest Washington, has full-time and part-time opportunities in general family practice or urgent care for BC/BE Family Physicians and Internists in the Portland/Vancouver and Salem, OR areas and Longview, WA. In Salem, opportunities exist for Family Physicians or Internists with a special interest or expertise in geriatrics.

Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest and a competitive salary/benefits package. **Forward inquiry and C.V. to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah Street, Suite 100, Portland, OR 97232-2099. EOE.**

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HOSPITAL BASED INTERNIST SOUGHT TO PROVIDE NIGHT COVERAGE for flourishing primary care practice in a growing coastal community in North Carolina. Area hospitals have University affiliation with UNC-Chapel Hill and Duke. Excellent industrial base; 8,435 student university campus; family oriented community with year-round sailing, golfing, fishing, tennis, and miles of beautiful beaches. Full benefit package, competitive salary. EOE. CV to Patrick Medeiros, Human Resources, Wilmington Health Associates, PO Box 4186, Wilmington, NC 28406.

FAMILY PRACTITIONER TO JOIN A FLOURISHING PRIMARY CARE PRACTICE in a 40-physician multispecialty group established for 25 years in community. Growing area of coastal North Carolina, 250,000 referral area. 628-bed tertiary care, university affiliated (UNC-Chapel Hill) hospital. Excellent industrial base; 8,435 student university campus; family oriented community with year-round sailing, golfing, fishing; package, competitive salary. EOE. CV to Patrick Medeiros, Human Resources, Wilmington Health Associates, PO Box 4186, Wilmington, NC 28406.

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Well-established ambulatory care clinic. Benefit package, supportive staff, skilled ARNP/PA-C. Salary: guaranteed minimum, percentage. Abundant recreational activities.

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Send CV: 621 E Front St, Port Angeles, WA 98362.

General Internist/ER physician.

THE VA MEDICAL CENTER, LONG BEACH, CA is recruiting for a Staff Physician for the Emergency Room. Board Certification in Internal Medicine or Emergency Medicine with some Emergency Room experience is necessary. Hours consist exclusively of evenings and nights, including weekends and holidays. Duties include direct patient care, teaching, and supervision of house staff. VAMC, Long Beach, is affiliated with the College of Medicine at the University of California, Irvine. Please send CV to:

David Webb, MD, Associate Chief of Staff, Ambulatory Care Service (153), VA Medical Center, 5901 E 7th Street, Long Beach, CA 90822.
Equal Opportunity Employer.

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FAMILY PRACTICE

Northern California multispecialty group has immediate opening. Clinical activities involve full range of Family Practice **outpatient and inpatient practice.** Abundant recreational opportunities and small town living. Competitive salary and comprehensive benefit package. CV to: **10978 Donner Pass Rd, Truckee, CA 96161.**

PART-TIME MEDICAL CONSULTANT CONTRACTS. Physicians needed to work under contract on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 75 Hawthorne Street, San Francisco. No patient contact. Applicants must: (1) have a valid license to practice medicine in the USA: (2) have current or recent clinical experience; and (3) be available between 6:30 AM and 5:30 PM, Monday through Friday, for case review. Subject to change, the specialties needed are Internal Medicine, Pediatrics, Orthopedics/Physiatry, Psychiatry, and Cardiology. The expected date of contract is 10-1-95. In addition, there is a need for a Regional Medical Advisor. This is an administrative position. As well as meeting 1, 2, and 3 above, applicants must have at least 5 years' experience working for the Social Security Administration's Disability Programs Branch. Women and minorities are encouraged to apply. If interested in receiving further information, submit written request by April 5, 1995, to: Contracting Officer, 50 United Nations Plaza, Room 403, San Francisco, CA 94102

HOW ABOUT A WARMER CLIMATE? Some of the most progressive medical groups in the Southwest and California want us to find exceptional BC/BE primary care physicians for permanent and Locum Tenens positions. Top benefits, profit sharing, guarantee plus incentive pay. Please call Catalina Professional Recruiters, Inc, in Tucson: (800) 658-9166, FAX (520) 322-2676; or in Phoenix: (800) 657-0354, FAX (602) 433-9548.

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GENERAL INTERNIST TO JOIN EIGHT GENERAL INTERNISTS IN A FLOURISHING 40-physician multispecialty group practice. Growing area of coastal North Carolina; 250,000 referral area. 628-bed tertiary care, university affiliated (UNC-Chapel Hill) hospital. Excellent industrial base; 8,435 student university campus; family oriented community with year-round sailing, golfing, fishing, tennis, and miles of beautiful beaches. Full benefit package, competitive salary. EOE. CV to Patrick Medeiros, Human Resources, Wilmington Health Associates, PO Box 4186, Wilmington, NC 28406.

CALIFORNIA: SAN JOSE AREA. New opportunity at five Good Samaritan Health System Occupational Medicine Clinics. Physicians with Occupational Medicine, ER, Internal Medicine, or Family Practice experience (preferably Board Certified) who are interested in making a long-term commitment should send CVs to: T.A. Foster, MD, FACPM, 2577 Samaritan Dr, Ste 760, San Jose, CA 95124. Phone (408) 358-1074, FAX (408) 358-1764. Fluency in Spanish and/or Vietnamese is a plus. EEO employer. Excellent benefits. Competitive salary.

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FAMILY PRACTICE PHYSICIANS. Opportunities available at busy migrant/indigent medical clinics located in Central Washington and Northeastern Oregon. Opportunities are available at all five of our clinics located in Yakima, Toppenish, Grandview, and Walla Walla, WA and Hermiston, OR. YVFWC has over 45 clinicians specialized in Family Practice, Pediatrics, OB/GYN, and Internal Medicine as well as nine dentists. Excellent benefits provided, including paid malpractice, CME and license/DEA renewal. NHSC and state loan repayment available. Contact: Mayling Chin, Recruiting Specialist, PO Box 190, Toppenish, WA 98948. Telephone: (509) 865-5898. FAX: (509) 865-4337.

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OPPORTUNITIES AVAILABLE IN NORTHERN NEW MEXICO FOR BOTH FULL AND PART TIME Emergency Room physicians. Must be BC/BE with current ACLS and/or ATLS. Join a hospital-based group providing services to the Espanola Hospital, which is located in the Rio Grande Valley between Santa Fe and Taos. Position offers employment with competitive benefits. Please send CV to Bill Norris, Presbyterian Healthcare Services, PO Box 26666, Albuquerque, NM 87125, or contact (800) 545-4030 Ext. 6320.

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Opportunities available in Northern New Mexico

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or contact at 1-800-545-4030, ext. 6320

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Excellent employment opportunity for the right physician. The community of Clovis, New Mexico is seeking a physician to head its urgent care operation located in the Clovis High Plains Regional Hospital.

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For information, contact Bill Norris at 1-800-545-4030, ext. 6320, or mail your CV to Presbyterian Healthcare Services, P.O. Box 2666, Albuquerque, NM 87125

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The CMO will be a UCSF faculty member at an Assistant or Associate Clinical Professor level, depending on experience and qualifications. UCSF is an Equal Opportunity/ Affirmative Action Employer. Women and minorities are encouraged to apply. Send CV, summary of clinical interests and three references to: John Balmes, MD; Chair, Search Committee; Chief, Division of Occupational and Environmental Medicine; UCSF, Box 0843, San Francisco, CA 94143-0843. (Please reference Search M-1551.)

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LOVELACE HEALTH SYSTEMS

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ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

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NORTHWEST REGION

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- INTERNAL MEDICINE
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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-7, 1995, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

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Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 27-30, 1995, Resort at Squaw Creek, 1995.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. May 12-13, 1995, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 27-30, 1995. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 28-30, 1995. Spokane Sheraton Hotel, Spokane, Washington.

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- Laparoscopically Assisted Colectomy: Surgeons can now effectively remove segments of the colon through this minimally invasive technique.

The Center's comprehensive services include:

- Colonoscopy
- Management of recurrent colorectal cancer
- Anorectal physiologic studies
- Evaluation of continence disorders
- Continence preserving and restoring surgical procedures
- Post-operative pain management, rehabilitation and education
- Research activities including the physiology of continence and surgical techniques
- Educational activities to support physicians in the development of current surgical techniques

Center surgeons perform all major surgeries at USC University Hospital or USC/Norris Cancer Center. Both facilities provide the latest in technology, patient care and dedicated colorectal trained nurses.

Physician Support and Education

As an academically based program, the Center is dedicated to providing continuing education and support for physicians practicing in the community setting. Physicians are encouraged to contact USC PACE for patient consultation or program information.

About the Director

Robert W. Beart, Jr., M.D., *Professor of Surgery at the USC School of Medicine, serves as Director of the USC Center for Colorectal Diseases. He is a world-renowned specialist in colon and rectal surgery, with extensive experience in performing and refining surgical alternatives to ileostomy and colostomy and laparoscopic colon resection.*

Dr. Beart received his medical degree from Harvard Medical School, and completed his internship and residencies at the University of Colorado Medical Center in Denver. He did a transplant fellowship (liver and kidney) at the University of Colorado, and a colon and rectal fellowship at the Mayo Clinic Rochester. For more than a decade, he served as Chairman, Colon and Rectal Surgery at the Mayo Clinic Rochester, and was named the Caywood Professor of Surgery. At the Mayo Clinic Scottsdale (Arizona), he was Chairman, Department of General Surgery. He joined USC University Hospital in 1992.

Dr. Beart, a member of numerous professional organizations, is the immediate Past President of the American Society of Colon and Rectal Surgeons. He is widely published in peer review journals, is the editor of Diseases of the Colon & Rectum, *and is a much sought after lecturer.*

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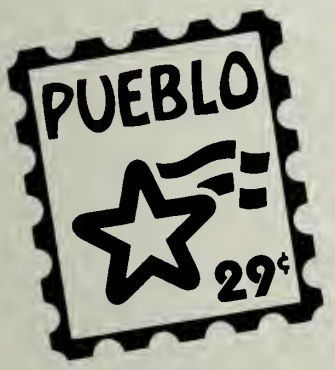

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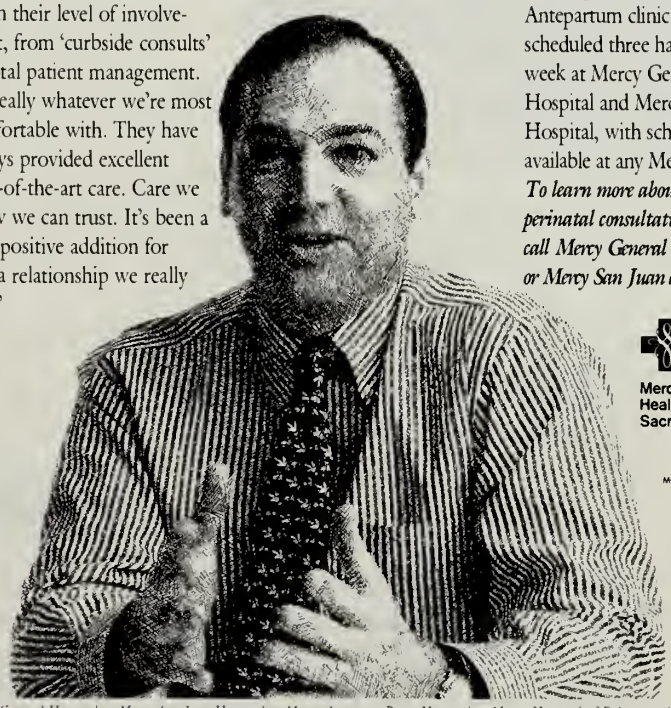

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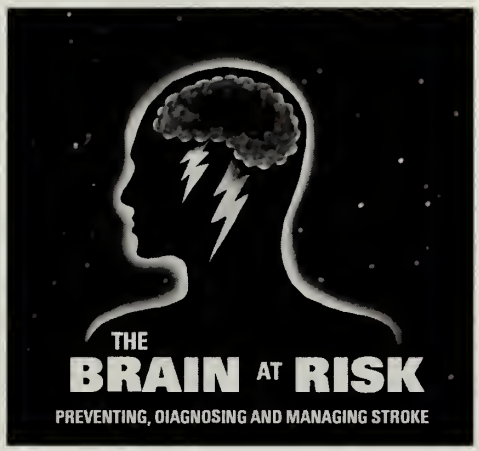

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Anderson CM: Sodium chloride treatment of amphotericin B nephrotoxicity—Standard of care? West J Med 1995; 162:313-317)

Amphotericin B is an effective therapeutic agent for most systemic or invasive mycoses, but its usefulness is limited by the frequent occurrence of nephrotoxicity. Given the high and increasing frequency of serious fungal infections, especially in immunocompromised patients, the importance of the morbidity caused by this toxicity is substantial. Salt loading may prevent and even reverse amphotericin B-induced azotemia by an unknown mechanism. A prospective, randomized, placebo-controlled trial in a relevant patient group would strengthen the support for this simple, safe therapy, but will not likely be carried out because of practical and ethical considerations. Thus, a few prospective and limited controlled human studies may be the only supportive evidence for using this therapy. Supplementing dietary sodium chloride intake with 150 mEq of sodium chloride daily intravenously or orally beginning when or before amphotericin B therapy is initiated will likely prevent much of the observed nephrotoxicity and should be carried out routinely.

SODIUM CHLORIDE TREATMENT NEPHROTOXICITY
AMPHOTERICIN B NEPHROTOXICITY

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SODIUM CHLORIDE TREATMENT NEPHROTOXICITY
AMPHOTERICIN B NEPHROTOXICITY

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In Memoriam

California Medical Association

Bell, Taine T., Watsonville. Died Feb 5, 1995, aged 77. Graduate of Stanford University School of Medicine, Stanford, California, 1947. Licensed in California in 1947. Dr Bell was a member of the Santa Cruz County Medical Society.

❧

Fuller, Thomas Patrick, Mountain View. Died Feb 27, 1995, aged 63. Graduate of Ohio State University College of Medicine, Columbus, 1958. Licensed in California in 1961. Dr Fuller was a member of the Santa Clara County Medical Association.

❧

Henry, John R., Oakland. Died Nov 9, 1994, aged 93. Graduate of University of California, San Francisco, School of Medicine, 1929. Licensed in California in 1929. Dr Henry was a member of the Alameda-Contra Costa Medical Association.

❧

Layton, Benjamin J., San Diego. Died Dec 30, 1994, aged 73. Graduate of Stanford University School of Medicine, Stanford, California, 1955. Licensed in California in 1956. Dr Layton was a member of the San Diego County Medical Society.

❧

Leeds, Sanford E., San Francisco. Died Feb 27, 1995, aged 85. Graduate of University of California, San Francisco, School of Medicine, 1936. Licensed in California in 1936. Dr Leeds was a member of the San Francisco Medical Society.

❧

McLinden, John W., Los Gatos. Died Jan 28, 1995, aged 75. Graduate of University of Minnesota Medical School, Minneapolis, 1951. Licensed in California in 1953. Dr McLinden was a member of the Santa Clara County Medical Association.

❧

Mehalko, Steven G., San Francisco. Died Jan 24, 1995, aged 45. Graduate of Boston University School of Medicine, Boston, Massachusetts, 1973. Licensed in California in 1977. Dr Mehalko was a member of the San Francisco Medical Society.

❧

Miles, Howard C., Salinas. Died Jan 26, 1995, aged 75. Graduate of Northwestern University Medical School, Chicago, Illinois, 1943. Licensed in California in 1946. Dr Miles was a member of the Monterey County Medical Society.

Quick, E. Danford., Riverside. Died Feb 15, 1995, aged 83. Graduate of University of Minnesota Medical School, Minneapolis, 1937. Licensed in California in 1941. Dr Quick was a member of the Riverside County Medical Association.

❧

Ringrose, Edward, Berkeley. Died Jan 21, 1995, aged 83. Graduate of University of Iowa College of Medicine, Iowa City, 1939. Licensed in California in 1939. Dr Ringrose was a member of the Alameda-Contra Costa Medical Association.

❧

Schnoor, Thomas G., Santa Cruz. Died Feb 1, 1995, aged 86. Graduate of Duke University School of Medicine, Durham, NC, 1939. Licensed in California in 1943. Dr Schnoor was a member of the Santa Cruz County Medical Society.

❧

Shaskan, Donald A., San Francisco. Died Jan 5, 1995, aged 84. Graduate of New York University School of Medicine, New York, 1934. Licensed in 1948. Dr Shaskan was a member of the San Francisco Medical Society.

❧

Watts, Donald G., Berkeley. Died Jan 27, 1995, aged 87. Graduate of University of California, San Francisco, School of Medicine, 1943. Licensed in California in 1943. Dr Watts was a member of the Alameda-Contra Costa Medical Association.

❧

Whisenand, James M., La Jolla. Died Dec 16, 1994, aged 72. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1946. Licensed in California, 1994. Dr Whisenand was a member of the San Diego County Medical Society.

❧

Zirkle, Thomas I., San Bernardino. Died Jan 29, 1995, aged 92. Graduate of Loma Linda University School of Medicine, Los Angeles, 1928. Licensed in California in 1928. Dr Zirkle was a member of the San Bernardino County Medical Society.

New Mexico Medical Society

Sheppeck, Michael L., Farmington. Died Nov 9, 1994, aged 84. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1936. Licensed in New Mexico in 1978. Dr Sheppeck was a member of the San Juan County Medical Society.

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From the Department of Medicine, University of California, Los Angeles, School of Medicine.

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Onset of action as early as 12 hours[3]

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Excellent safety profile

No measurable effect on HPA function at recommended doses[4,5]

The most commonly reported side effects are headache and nasal irritation

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Nasacort® Nasal Inhaler

(triamcinolone acetonide)

Please see brief summary of prescribing information on following page.

1 ONCE DAILY Nasacort® Nasal Inhaler

(triamcinolone acetonide)

For Intranasal Use Only
Shake Well Before Using
BRIEF SUMMARY
CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of this preparation contraindicates its use
WARNINGS: The replacement of a systemic corticosteroid with a topical corticoid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticoids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms
Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered
The use of Nasacort Nasal Inhaler with alternate-day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Nasacort Nasal Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease
PRECAUTIONS
General: In clinical studies with triamcinolone acetonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local therapy and discontinuance of treatment with Nasacort Nasal Inhaler
Triamcinolone acetonide administered intranasally has been shown to be absorbed into the systemic circulation in humans. Patients with active rhinitis showed absorption similar to that found in normal volunteers. Nasacort at 440 mcg/day for 42 days did not measurably affect adrenal response to a six hour cosyntropin test. In the same study prednisone 10 mg/day significantly reduced adrenal response to ACTH over the same period (see CLINICAL TRIALS section).
Nasacort Nasal Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex
Because of the inhibitory effect of corticosteroids on wound healing in patients who have experienced recent nasal septal ulcers, nasal surgery or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances
When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasacort Nasal Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy
Information for Patients: Patients being treated with Nasacort Nasal Inhaler should receive the following information and instructions.
Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice
Patients should use Nasacort Nasal Inhaler at regular intervals since its effectiveness depends on its regular use. A decrease in symptoms may occur as soon as 12 hours after starting steroid therapy and generally can be expected to occur within a few days of initiating therapy in allergic rhinitis. The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Nasal irritation and/or burning or stinging after use of the spray occur only rarely with this product. The patient should contact the physician if they occur
For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully. Because the amount dispensed per puff may not be consistent, it is important to shake the canister well. Also, the canister should be discarded after 100 actuations
Carcinogenesis, Mutagenesis: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of 1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice
Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5 - 15.0 mcg/kg/day or 20 - 110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).
Pregnancy: Pregnancy Category C. Like other corticoids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08, and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51, and 318.7 times the minimum recommended dose of 110 mcg of Nasacort per day and 3.2, 6.4, 12.7, and 80 times the maximum recommended dose of 440 mcg of Nasacort per day based on a patient body weight of 70 kg. Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Experience with oral corticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy
Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed
Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Nasacort Nasal Inhaler is administered to nursing women.
Pediatric Use: Safety and effectiveness have not been established in children below the age of 12. Oral corticoids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.
ADVERSE REACTIONS: In controlled and uncontrolled studies, 1257 patients received treatment with intranasal triamcinolone acetonide. Adverse reactions are based on the 567 patients who received a product similar to the marketed Nasacort canister. These patients were treated for an average of 48 days (range 1 to 117 days). The 145 patients enrolled in uncontrolled studies received treatment from 1 to 820 days (average 332 days)
The most prevalent adverse experience was headache, being reported by approximately 18% of the patients who received Nasacort. Nasal irritation was reported by 2.8% of the patients receiving Nasacort. Other nasopharyngeal side effects were reported by fewer than 5% of the patients who received Nasacort and included: dry mucous membranes, naso-sinus congestion, throat discomfort, sneezing, and epistaxis. The complaints do not usually interfere with treatment and in the controlled and uncontrolled studies approximately 1% of patients have discontinued because of these nasal adverse effects
In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).
OVERDOSAGE: Acute overdosage with this dosage form is unlikely. The acute topical application of the entire 15 mg of the canister would most likely cause nasal irritation and headache. It would be unlikely to see acute systemic adverse effects if the nasal application of the 15 mg of triamcinolone acetonide was administered all at once
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Please see product circular for full prescribing information

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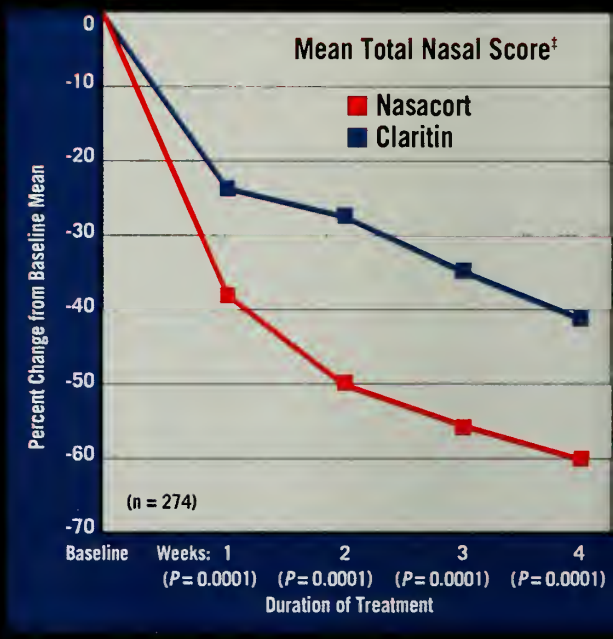
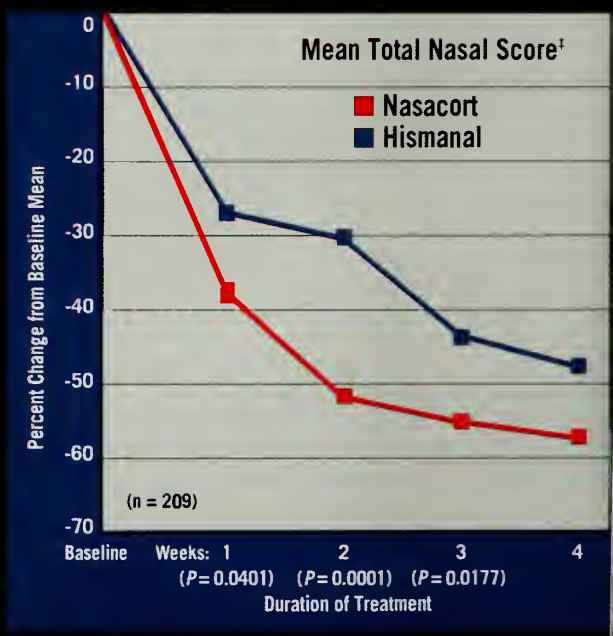


‡ *Total nasal score is the sum of nasal congestion, rhinorrhea, postnasal drip, sneezing, and nasal itch.*

NASACORT VS. HISMANAL[2]†



* *Claritin (loratadine) is a registered trademark of Schering Corporation.*
† *Each study was a double-blind, randomized, multicenter, parallel group, controlled study divided into a screening period of up to 28 days which included a drug-free baseline period (the last 5 days of the screening period) and a double-blind active treatment period of 4 weeks (28 days).*
§ *Hismanal (astemizole) is a registered trademark of Janssen Pharmaceutica Inc.*

REFERENCES

1. Data on file, Protocol RG-5029-604 (Nasacort vs. Claritin), Rhône-Poulenc Rorer Pharmaceuticals Inc. 2. Data on file, Protocol RG-5029-603 (Nasacort vs. Hismanal), Rhône-Poulenc Rorer Pharmaceuticals Inc. 3. Data on file, Protocol CTA 0393 (triamcinolone acetonide vs. placebo), Rhône-Poulenc Rorer Pharmaceuticals Inc. 4. Ziemniak JA: Pharmacokinetics of intranasal triamcinolone acetonide. J Respir Dis 1991;12(3, Suppl): S41-S42. 5. Feiss G, Morris R, Rom O, et al: A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. J Allergy Clin Immunol 1992;89(6):1151-1156.

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ABSTRACTS APRIL 1995

(Abrass CK: Diabetic nephropathy—Mechanisms of mesangial matrix expansion. West J Med 1995; 162:318-321)

Diabetic nephropathy, a major cause of morbidity and mortality in patients with diabetes mellitus, is characterized by the progressive expansion of mesangial matrix that ultimately occludes glomerular capillaries. Multiple factors in the abnormal metabolic milieu of diabetes contribute to the development of increased amounts of mesangial matrix. Glucose stimulates an increase in synthesis of most collagens and matrix glycoproteins normally expressed within the mesangium. Abnormal glycosylation of matrix proteins interferes with their degradation and turnover. Periods of hyperinsulinemia and alterations in angiotensin II induce changes in the phenotype of mesangial cells and the composition of matrix they secrete. Together, glucose, insulin, and angiotensin II conspire to produce an unrelenting increase in accumulation of mesangial matrix, with altered composition and function.

DIABETES MELLITUS
DIABETIC NEPHROPATHY
MESANGIAL CELLS

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ABSTRACTS APRIL 1995

(Aron DC, Tyrrell JB, Wilson CB: Pituitary tumors—Current concepts in diagnosis and management. West J Med 1995; 162:340-352)

Diagnostic advances have resulted in earlier and more frequent recognition of pituitary tumors. Pituitary tumors cause problems owing to the hormones they secrete or the effects of an expanding sellar mass—hypopituitarism, visual field abnormalities, and neurologic deficits. Prolactin-secreting tumors (prolactinomas), which cause amenorrhea, galactorrhea, and hypogonadism, constitute the most common type of primary pituitary tumors, followed by growth hormone-secreting tumors, which cause acromegaly, and corticotropin-secreting tumors, which cause Cushing's syndrome. Hypersecretion of thyroid-stimulating hormone, the gonadotropins, or α-subunits is unusual. Nonfunctional tumors currently represent only 10% of all clinically diagnosed pituitary adenomas, and some of these are α-subunit–secreting adenomas. Insights into the pathogenesis and biologic behavior of these usually benign tumors have been gained from genetic studies. We review some of the recent advances and salient features of the diagnosis and management of pituitary tumors, including biochemical and radiologic diagnosis, transsphenoidal surgery, radiation therapy, and medical therapy. Each type of lesion requires a comprehensive but individualized treatment approach, and regardless of the mode of therapy, careful follow-up is essential.

PITUITARY TUMORS **PROLACTINOMAS**
PITUITARY ADENOMAS

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:
Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS–*Liver*).
Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Augmentin should not be coadministered with Antabuse® (disulfiram).
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient. <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS). A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
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Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. 2. *Clinical Efficacy Update II*, SmithKline Beecham Pharmaceuticals, 1994.

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Articles

Sodium Chloride Treatment of Amphotericin B Nephrotoxicity

Standard of Care?

CLAY M. ANDERSON, MD, *Houston, Texas*

Amphotericin B is an effective therapeutic agent for most systemic or invasive mycoses, but its usefulness is limited by the frequent occurrence of nephrotoxicity. Given the high and increasing frequency of serious fungal infections, especially in immunocompromised patients, the importance of the morbidity caused by this toxicity is substantial. Salt loading may prevent and even reverse amphotericin B-induced azotemia by an unknown mechanism. A prospective, randomized, placebo-controlled trial in a relevant patient group would strengthen the support for this simple, safe therapy, but will not likely be carried out because of practical and ethical considerations. Thus, a few prospective and limited controlled human studies may be the only supportive evidence for using this therapy. Supplementing dietary sodium chloride intake with 150 mEq of sodium chloride daily intravenously or orally beginning when or before amphotericin B therapy is initiated will likely prevent much of the observed nephrotoxicity and should be carried out routinely.

(Anderson CM: Sodium chloride treatment of amphotericin B nephrotoxicity—Standard of care? West J Med 1995; 162:313-317)

The polyene antibiotic amphotericin B is a crucial agent in the management of serious systemic fungal infections, despite its well-known side effects and toxicities. Published studies show that fungal organisms are identified in 1% to 12% of patients admitted to a hospital and that fungal infections account for about 5% of cases of primary septicemia.[1] Between 1980 and 1990, the incidence of fungal infections in inpatients doubled, the nosocomial fungemia rate rose fivefold, and the proportion of nosocomial infections caused by fungi rose from 6% to 10%.[2] Given the large and increasing number of immunocompromised patients, such as allogeneic transplant recipients, chemotherapy patients, and persons infected with the human immunodeficiency virus, many of whom need to be treated with amphotericin B for either empirical or microbiologically confirmed indications, the use of this antimicrobial agent will have a prominent role for the foreseeable future.

Serious nephrotoxicity develops in as many as 80% of patients receiving a full course of amphotericin B,[3] which often can delay initiating or necessitate terminating therapy despite a life-threatening systemic fungal infection. Rates of toxicity as low as 25% have also been reported.[4] As evidenced by a recent toxicity prevention trial that showed a rate of nephrotoxicity of 75% in the control group and 28% in an intervention group, the rate of toxicity does not appear to have declined in recent years.[5] In general, the degree of renal toxicity correlates with the daily or cumulative dose of amphotericin B, leading to the conclusion that total doses in excess of 3 grams are toxic in the vast majority of patients.[6,7] Renal abnormalities induced by amphotericin B include azotemia associated with a decreased glomerular filtration rate (GFR) and renal blood flow, diminished concentrating ability, defective urinary acidification, and potassium wasting. The mechanism of nephrotoxicity is unknown, but may relate to the ionophore properties of amphotericin B on biologic membranes.[8] Despite encouraging studies in animals and widespread clinical use in the past, the use of mannitol has been shown in a double-blind, prospective study not to prevent this nephrotoxicity.[9]

A review in 1988 cited data from studies of animals and limited human studies to support sodium loading as therapy for amphotericin B nephrotoxicity.[10] Since then, further human studies, including prospective and controlled trials, have shown the effectiveness of this therapy, but sodium loading has not gained wide acceptance as routine practice despite continued substantial nephrotoxicity. I will review this more recent evidence and make a case for the routine use of this therapy as a standard of care.

Studies of Animals and In Vitro Studies

Work in dogs has suggested that amphotericin B nephrotoxicity is caused by enhanced tubuloglomerular

From the Department of Medicine, University of Colorado Health Sciences Center, Denver. Dr Anderson is now with the Department of Medicine, MD Anderson Cancer Center, Houston, Texas.

Reprint requests to Clay M. Anderson, MD, Dept of Medicine, MD Anderson Cancer Center, Box 010, 1515 Holcombe, Houston, TX 77030.

ABBREVIATIONS USED IN TEXT

GFR = glomerular filtration rate
TGF = tubuloglomerular feedback

feedback (TGF) due to the drug.[11] Tubuloglomerular feedback is a normal intrarenal mechanism whereby increased solute delivery to the distal tubule for whatever reason results in afferent arteriolar vasoconstriction. The rationale for this mechanism is thought to be the prevention of electrolyte and water losses under varying conditions. According to this hypothesis, amphotericin B, possibly because of its effects on biologic membranes, increases monovalent ion delivery to the distal tubule, causing afferent arteriolar vasoconstriction, most likely due to local adenosine release. It was shown that TGF can be blocked by salt loading or administering furosemide or theophylline. Other mechanisms of amphotericin B nephrotoxicity suggested in the literature are direct toxic effects to the afferent arterioles and tubules[3,12] and direct renal and systemic vasoconstriction.[13]

A detailed physiologic study on rats in 1991 shed light and provoked controversy on the mechanism of amphotericin B nephrotoxicity.[13] Single-nephron studies carried out with micropuncture techniques were used to assess the effects of amphotericin B on proximal and distal tubule flow rates. According to the hypothesis, if amphotericin B enhances TGF, it should increase distal tubule solute delivery, resulting in a macula densa signal that thereby causes afferent arteriolar vasoconstriction. This effect should be apparent in a greater decrease in the single-nephron GFR when measured distally (downstream from the macula densa) than when measured proximally (upstream from the macula densa signal) in the presence of amphotericin B. Measured before and after amphotericin B infusion, the single-nephron GFRs in proximal and distal tubules were decreased similarly in both regions, leading the investigators to conclude that direct TGF activation may not be the mechanism for the observed nephrotoxicity. They also showed systemic and afferent arteriolar vasoconstriction by amphotericin B that was calcium-dependent but endothelium-independent and that was blocked by atrial natriuretic peptide and theophylline. The roles of atrial natriuretic peptide and nitric oxide in the local regulation of renovascular tone have been characterized,[14,15] and these may represent alternative sites for changes in renal function caused by amphotericin B.

Another study showed that sodium chloride loading in rats starting three days before amphotericin B was given prevented the rise in serum creatinine levels during long-term amphotericin B adminstration that occurred in a non–salt-supplemented group.[16] The preservation of renal perfusion and GFR was demonstrated in the saline-fed rats relative to the water-fed rats. Salt loading, however, did not prevent the development of tubular defects, including decreased concentrating ability, diminished acidification, and potassium wasting. Final body weights were similar in both groups. In rats not receiving amphotericin B, salt loading did not affect renal perfusion or GFR. The authors postulated different toxicity mechanisms for the decreased GFR and tubular defects. In light of these findings, the conclusions discussed earlier may have been confounded by direct or indirect tubular effects interfering with the measured vascular effects—that is, TGF versus direct vasoconstriction.

Human Studies of Sodium-Loading Therapy

The five published studies of sodium-loading therapy during amphotericin B therapy are summarized in Table 1.[4,17-19] In 1983 the cases of five patients with impaired renal function early in the course of amphotericin B therapy

TABLE 1.—*Human Trials of Salt Loading for Prophylaxis of Amphotericin B Nephrotoxicity*

Patients, No.	*Design and Source*	*Made af Therapy*	*Dose, mEq/day*	*Amphotericin B Dase*	*Outcame*	*P Value*
5	Case series; Heidemann et al, 1983[17]	PO or IV NaCl	150-600	25 mg/day target	Improved serum Cr, continuing amphotericin B	NA
38	Retrospective; Branch et al, 1987[18]	IV ticarcillin	100-150	25 mg/day target	Increase in serum Cr*	<.01
20	Prospective; Branch et al, 1987[18]	IV NaCl	150	40 mg/day target	Increase in serum Cr*	NA
37	Prospective; Arning and Scharf, 1989[4]	IV NaCl	85-171	231-7,831 mg over 9-136 days	Increase in serum Cr*	NA
20	Placebo-controlled; Llanos et al, 1991[19]	IV NaCl	150	1,500 mg in 10 weeks	Cr clearance preserved	<.01

Cr = creatinine, IV = intravenous, NA = not available, NaCl = sodium chloride, PO = oral

*Increase in serum creatinine levels to >180 μmol/liter (>2.0 mg/dl) or to >2 times the baseline value, but less than before therapy.

who had improvement in renal function with sodium loading were described.[17] The patients received between 150 and 600 mEq of sodium chloride in intravenous or oral form daily in addition to their dietary intake. All the patients were then able to finish their amphotericin B course along with sodium supplementation, and renal function was preserved. These five patients were immunocompromised and had systemic fungal infections, but they did not have cancer or neutropenia. Four of the five were thought clinically to have hypovolemia before therapy. The ability of salt loading to inhibit TGF and improve the GFR in dogs was the rationale for the intervention in these patients.

In 1987 retrospective and prospective studies in Nashville, Tennessee, and Essen, Germany, showed that salt supplementation was associated with a lower incidence of amphotericin B nephrotoxicity.[18] In the retrospective study, the rate of nephrotoxicity was 67% (14 of 21) of patients without salt supplementation and 12% (2 of 17) of patients with concurrent ticarcillin therapy (100 to 150 mEq of sodium per day), with a target amphotericin B dose of 25 mg per day ($P < .01$). Nephrotoxicity subsequently developed in four patients who had their ticarcillin stopped, and one patient who had nephrotoxicity without ticarcillin therapy showed improved renal function after the initiation of intravenous sodium chloride therapy. In a prospective series at Essen, only 2 cases of nephrotoxicity occurred in 20 patients receiving amphotericin B at a target dose of 40 mg per day with the use of 150 mEq of sodium chloride per day as an intravenous infusion. There was no control group in this series. Most of the patients in both these studies had acute leukemia and were receiving many other medications.

An open, prospective, uncontrolled trial in 1989 showed that prophylactic sodium loading with 85 to 171 mEq of sodium chloride per day resulted in a 0% incidence of notable nephrotoxicity (an increase in serum creatinine levels to >180 μmol per liter [>2.0 mg per dl] or to a level more than double the baseline value) among 37 patients receiving between 231 and 7,831 mg of amphotericin B.[4] A minimum urine output was assured in all of these patients. Among the 37 patients, 11 had a transient rise in serum creatinine levels to more than 124 μmol per liter (1.4 mg per dl), but none had values greater than 180 μmol per liter or double their baseline values. All but one of these patients suffered from malignant hematologic disorders. A control group was not considered to be ethically appropriate for this trial, based on the high incidence of toxicity without therapy.

The only prospective, double-blind, placebo-controlled trial done to assess the protective effects of sodium chloride loading in amphotericin B-induced nephrotoxicity was reported in 1991.[19] The investigators studied 20 male patients in Peru who were being treated with 50 mg of amphotericin B three times per week for 10 weeks for mucocutaneous leishmaniasis. These were healthy men with a high baseline daily sodium intake (262 ± 23 mEq per day in the control group and 243 ± 17 mEq per day in the saline-treated group). Ten subjects were given 1 liter of a 5% dextrose solution intravenously before the amphotericin B therapy, and 10 were given 1 liter of a 0.9% sodium chloride solution intravenously. The groups were similar at baseline, except that the control group had slightly lower baseline serum creatinine levels—53 versus 71 μmol per liter (0.6 versus 0.8 mg per dl). Serum creatinine levels rose and creatinine clearances decreased significantly in the dextrose-treated group compared with the saline-treated group (10-week creatinine level, 88 versus 71 μmol per liter [1.0 versus 0.8 mg per dl]; 10-week creatinine clearance, 1.27 versus 1.52 ml per second per 1.73 m^2 [76 versus 91 ml per minute per 1.73 m^2], respectively; $P < .05$). Urinary sodium excretion decreased in the dextrose-treated group, but was unchanged in the saline-treated group. Urinary specific gravity and urinary calcium excretion declined in both groups. A faster loss of acidifying ability occurred in the saline-treated group. Plasma amphotericin B concentrations were similar in the two groups. No adverse effects were noted in the saline- or dextrose-treated groups.

Discussion

The studies in animals and humans described here show convincingly that sodium loading in excess of the usual dietary intake notably reduces the incidence and severity of amphotericin B-induced nephrotoxicity and may reverse preexisting nephrotoxicity. The exact mechanism by which this beneficial effect occurs has not been elucidated. The theory that sodium chloride loading blocks amphotericin B-induced TGF seems to be in question, based on single-nephron studies. Amphotericin B-induced systemic and renal vasoconstriction appears to play an important part in the toxicity and may relate to the inhibition of nitric oxide or atrial natriuretic peptide systems or enhanced adenosine release in the kidneys. How sodium chloride loading could reduce the vasoconstricting effects of amphotericin B, especially if they are direct in nature, is not clear. Furthermore, sodium chloride loading does not prevent the tubular toxicity of amphotericin B.

Also, the vasoconstrictive effects of amphotericin B are clearly calcium-dependent. Thus, it makes sense to hypothesize that calcium channel antagonists might reduce amphotericin B nephrotoxicity. Indeed, this has been shown conclusively in a rat model using diltiazem for both short- and long-term dosing of amphotericin B,[20] and at least one author has suggested using these agents in patients.[21] Experience thus far in humans, however, appears to be limited to anecdotal reports, and therefore no firm recommendation can be made with regard to the use of calcium channel blockers.

Another interesting development in the investigation of amphotericin B toxicity is the incorporation of the drug into liposomes. Studies in animals and preliminary human studies show a higher therapeutic index for this form of the drug, allowing for higher doses for a given level of toxicity. In addition, one study using rabbits shows decreased nephrotoxicity for liposomal amphotericin B.[22] More research is needed on the use of this preparation in humans, but it may be an important step in reducing the high rate of nephrotoxicity.

No adverse or toxic reactions to sodium loading in diverse patient groups have been reported. This therapy might be expected to be harmful to patients with preexisting sodium or fluid overload or reduced left ventricular function. This has not been reported in the literature, despite the use of this therapy in a fair number of acutely ill patients. Better toxicity data would require a larger number of reported uses for this therapy.

A prospective, placebo-controlled trial testing the effectiveness of sodium chloride loading at reducing amphotericin B nephrotoxicity in a typical patient group receiving this drug has not been undertaken. The trial described earlier was originally designed to have a control group, but preliminary data suggested that substantial expected benefit and little or no toxicity from treatment made the inclusion of a control group ethically questionable.[4] As a result, only one controlled trial has been carried out.[19] In this trial, the patient characteristics, drug dose, and duration of therapy were not typical of standard use for invasive mycoses. The strength, consistency, and biologic plausibility of the available data in humans and animals, however, are compelling enough to justify routinely giving patients this therapy, allowing experience in a large number of patients to accumulate with the hope of preventing a great deal of possible morbidity.

Further investigation is needed to determine the best method for sodium supplementation. One goal is to determine the best route and dosage of sodium chloride for the greatest benefit with the fewest complications. Patients with preexisting sodium depletion such as aggressively treated patients with heart failure or cirrhosis may be more likely to benefit from more liberal sodium intake and parenteral supplementation, but these same patients may also be most likely to suffer adverse consequences. Another issue is the optimal timing of sodium chloride loading in relation to the amphotericin B administration—is pretreatment necessary, and if so, how long in advance of amphotericin B administration? What is the possible benefit of furosemide, calcium channel blockade, and liposomal amphotericin B preparations to increase the dose or ameliorate the toxicity of treatment? Last, can we design an ethically acceptable and practically feasible placebo-controlled trial in a more representative patient group, possibly using crossover methods or surrogate markers for toxicity to prevent needless morbidity?

Practical Guidelines

Most experience is with the intravenous infusion of 150 mEq of sodium chloride (1 liter of 0.9% sodium chloride solution) per day as either a bolus or a continuous infusion, in addition to the usual dietary intake, with an excellent safety profile. This therapy should probably be started at least a day before the amphotericin B regimen is initiated. Tubular defects will not be prevented, and thus careful electrolyte management must be assured. Oral sodium supplementation is probably effective as well, and high salt-containing drugs—including ticarcillin and intravenous flucytosine—probably provide effective sodium supplementation. Dietary sodium should not be restricted, and adequate urinary output should be ensured (>2 liters per day).

Conclusion

Strong circumstantial clinical evidence based on a handful of case, retrospective, and prospective studies and one placebo-controlled trial supports the use of sodium chloride supplementation to prevent and to treat amphotericin B–induced nephrotoxicity. Definitive clinical proof of efficacy with a placebo-controlled trial in a representative patient group is probably not forthcoming. The mechanism by which this protection occurs is not clear, but it may be that tubuloglomerular feedback is prevented or that afferent arteriolar vasoconstriction is inhibited, or both. The treatment is safe and easy to administer. The best route, dose, and timing of sodium chloride therapy to maximize benefit and minimize complications need to be determined. Also, the possible role of calcium channel antagonists and liposomal amphotericin B needs to be further investigated. In the meantime, we should probably be administering at least 150 mEq or 9 grams of sodium chloride per day intravenously to patients receiving standard-dose amphotericin B therapy who can safely tolerate this salt load.

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* * *

GRAND MAL

I'd rather say that it was cold
that morning, earth frozen hard—

a scuff of frost on the outside glass.
I'd rather write of the sky, less

like fur or hair than granite. I'd rather
speak of anything defined, distant—than

to remember the sound of his half-choked
scream coming from the downstairs bathroom.

That Mother did scream released me—
"Your father. . . hurry" her body a blur—

while I remember the door, opening
as he lashed, fought, then fell, silent—

toes curled under, fingers entwined
only to each other, and eyes rolling back

just far enough not to know us. I tell you—
it wasn't cold. I was in shorts, and his head lay heavy

against my bare thigh, lips dry between hard breaths
as I turned his face slowly, to find some position

even suggesting rest. A bird called out, surely
a robin—sound lifting through screen windows

across this muddy, lighted season. I listened
for my father, and not a word

would come from his open mouth—
tongue held tight in Mother's hand.

KATE HARRIS©
Sequim, Washington

Articles

Diabetic Nephropathy

Mechanisms of Mesangial Matrix Expansion

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Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 1994.

Diabetic nephropathy, a major cause of morbidity and mortality in patients with diabetes mellitus, is characterized by the progressive expansion of mesangial matrix that ultimately occludes glomerular capillaries. Multiple factors in the abnormal metabolic milieu of diabetes contribute to the development of increased amounts of mesangial matrix. Glucose stimulates an increase in synthesis of most collagens and matrix glycoproteins normally expressed within the mesangium. Abnormal glycosylation of matrix proteins interferes with their degradation and turnover. Periods of hyperinsulinemia and alterations in angiotensin II induce changes in the phenotype of mesangial cells and the composition of matrix they secrete. Together, glucose, insulin, and angiotensin II conspire to produce an unrelenting increase in accumulation of mesangial matrix, with altered composition and function.

(Abrass CK: Diabetic nephropathy—Mechanisms of mesangial matrix expansion. West J Med 1995; 162:318-321)

Glomerular hypertrophy and thickening of the glomerular basement membrane with proportional enlargement of the glomerular mesangium develop in all patients with diabetes mellitus.[1,2] Yet, persons destined to have end-stage renal disease from diabetes have progressive expansion of the mesangium, which ultimately occludes the glomerular capillaries.[2] Considerable attention has recently focused on factors present in the altered metabolic milieu of diabetes that lead to mesangial matrix expansion and altered mesangial cell function. Hyperglycemia, the hallmark of diabetes mellitus, is an obvious possible contributor to many complications of diabetes, including nephropathy. Although hyperglycemia alone induces glomerular hypertrophy and thickening of basement membranes, it is insufficient to cause progressive mesangial matrix expansion.[3] Other factors (such as insulin and angiotensin II) likely interact with hyperglycemia to alter the composition of the extracellular matrix (ECM) and contribute to the development of end-stage diabetic nephropathy.

The treatment of hyperglycemia with exogenous insulin protects patients from the acute morbidity and mortality of uncontrolled diabetes and slows the rate of progression of several complications of diabetes, including nephropathy.[4,5] Such treatment has not prevented the development of nephropathy, however. Although the goal of insulin therapy is to establish normal circulating insulin levels, this is usually not achieved. Most patients experience frequent periods of hyperglycemia and hyperinsulinemia. As a result, secondary changes in circulating and locally produced growth factors commonly occur. Diabetic nephropathy develops in this complex milieu over many years. Thus, it is likely that many factors in the disordered metabolism of imperfectly treated diabetes mellitus conspire to produce unrelenting mesangial matrix expansion and, ultimately, chronic renal failure.

Changes in the Kidneys

Shortly after the onset of hyperglycemia, whole-kidney and glomerular hypertrophy develop.[6,7] Thereafter, progressive thickening of the glomerular and tubular basement membranes occurs due to the increased accumulation of matrix proteins normally present in these structures.[6,8] Later, nonenzymatic glycosylation further alters basement membrane structure and affects the barrier function of the capillary wall.[9] These changes are consistently observed in humans and animals with either type I or type II diabetes mellitus, as well as in models where galactose is administered.[3] In models of insulin resistance and in diabetic animals given exogenous insulin, the mesangial matrix progressively expands.[6,10] A similar occurrence is noted in normal animals treated with insulin. The mesangium expands by the accumulation of proteins normally present in the mesangial matrix, and new interstitial collagens and ECM proteins are expressed (Figure 1).[6,11-13] These changes steadily progress so that the amount and

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ABBREVIATIONS USED IN TEXT

ECM = extracellular matrix
IGF-I = insulin-like growth factor I
mRNA = messenger RNA
TGF-β = transforming growth factor β

composition of the mesangial matrix is greatly changed by the late stages of disease manifested by the occlusion of adjacent capillary loops.[2,6] Current research is focused on understanding those factors present in the altered metabolic milieu of diabetes that cause these qualitative and quantitative changes in mesangial matrix proteins.

Mesangium

The mesangium provides the central support for the glomerular capillaries and is composed of mesangial cells and the ECM they secrete. Normal mesangial matrix is primarily composed of collagens IV and VI, laminin, fibronectin, thrombospondin, and chondroitin sulfate proteoglycans.[6] Considerable new information has expanded our knowledge of the importance of the ECM in providing structural support for tissues and in promoting changes in cellular differentiation and cell function (reviewed by Juliano and Haskill[14] and Lin and Bissell[15]). As this field has grown, it has become apparent that collagen IV, thrombospondin, laminin, and fibronectin are each protein families with multiple genes and alternatively spliced individual gene products. The selective expression of individual family members in different extracellular matrix compartments, as well as the regulation of isoform expression within an ECM compartment, has important consequences to cell function. For example, changes in the ratios of individual matrix proteins and the expression of specific isoforms results in a mesangial matrix with completely different structural and physical properties. Moreover, an altered ECM composition engages different sets of integrin and nonintegrin receptors, which ultimately changes cell function and cellular response to cytokines and growth factors.[14] The lesion of diabetic nephropathy includes an increased accumulation of collagen IV, fibronectin, laminin, and thrombospondin in addition to the new expression of interstitial collagens I and III and novel isoforms of fibronectin and laminin.[16,17] Although additional factors undoubtedly contribute to diabetic nephropathy, the roles of glucose, insulin, and angiotensin II in promoting mesangial changes will be the focus of this review.

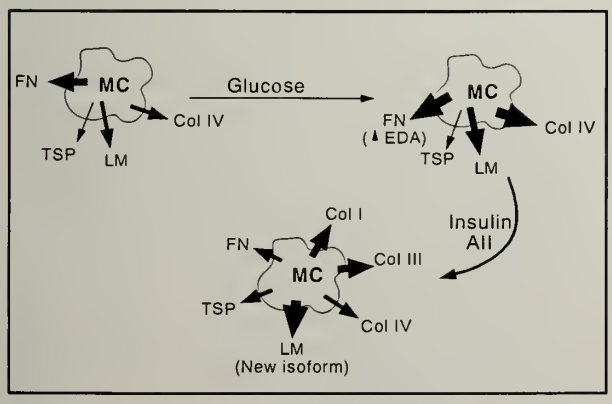

Figure 1.—The schema shows the effects of glucose, insulin, and angiotensin II (AII) on the amount and composition of extracellular matrix synthesized by mesangial cells (MC). The width of arrows indicates the relative amount synthesized. Col = collagen, EDA = extra domain A, FN = fibronectin, LM = laminin, TSP = thrombospondin

Regulation of Mesangial Cell Synthesis of Extracellular Matrix

Glucose

Elevated glucose levels slow the cellular proliferation of cultured mesangial cells and increase messenger RNA (mRNA) expression, protein synthesis, and protein accumulation of ECM proteins, including fibronectin, laminin, and collagens I, III, IV, and VI.[18-21] In a recent comprehensive study, glucose was shown to directly increase the rate of synthesis of all ECM proteins normally synthesized by the cell.[22] In addition, nonenzymatic glycosylation of ECM proteins was shown to slow the rate of degradation that would contribute to their accumulation in diabetes.[22] Glucose leads to an increase in diacylglycerol mass and activates protein kinase C.[23] Because diacylglycerol analogues and other activators of protein kinase C also increase ECM protein and mRNA expression by mesangial cells,[23,24] some of the direct effects of glucose on ECM synthesis appear to be through the protein kinase C pathway. In addition to the direct effects of hyperglycemia on ECM synthesis by mesangial cells, indirect effects also play a role. Hyperglycemia is associated with increased transforming growth factor-β (TGF-β) expression in mesangial cells, and TGF-β increases collagen IV and laminin synthesis.[16] These changes are partially corrected by insulin treatment.[16] These studies support a role for hyperglycemia in the increased synthesis of many ECM proteins that accumulate within the mesangium of diabetic kidneys. Improved glycemic control in patients with diabetes is therefore a necessary goal in the attempt to slow the rate of progression of diabetic renal disease.

Insulin

Studies of animals in our laboratory have shown that hyperglycemia is associated with an increased accumulation of ECM proteins normally present in the mesangium. Surprisingly, insulin treatment was found to induce a qualitative change in the collagenous composition of the ECM.[6] Because this suggested that insulin directly stimulates collagen synthesis, we examined mesangial cells in culture that were grown in the presence or absence of insulin. We found that high insulin concentrations (1 μmol per liter) stimulate mesangial cell proliferation[25,26] and cause the cells to synthesize predominantly collagens I and III.[26-28] In contrast, mesangial cells grown in the absence of insulin produce primarily collagen IV, which more closely resembles normal mesangial

matrix composition. An interesting finding was that mesangial cells that were established with insulin, but later had the insulin withdrawn, failed to synthesize the normal collagen pattern—that is, predominantly collagen IV. Thus, insulin was not only responsible for the changes in collagen expression, but the prolonged effect confirmed that the cells had undergone a phenotypic change. The finding that mesangial cells express abundant insulin receptors when propagated in media free of insulin further supports the notion that insulin and not the structurally related insulin-like growth factors (IGFs) initiated the change in collagen expression.

In addition to changes in collagen composition, diabetic nephropathy is associated with changes in the isoform of fibronectin and laminin that accumulates within the mesangium. The accumulation of the extra domain A–containing isoform of fibronectin has been shown in diabetic animals and in humans to have been influenced by glucose and insulin treatment.[16] Furthermore, we have shown that treating mesangial cells in culture with insulin induces a shift in the isoform of laminin that is synthesized.[17] Studies of laminin isoform in the mesangium in diabetic nephropathy have not been conducted. Based on the preceding data, we think that mesangial cells are responsive to physiologic concentrations of insulin and that during periods of hyperinsulinemia, insulin-mediated changes in ECM amount and composition occur. Like the results of the Diabetes Control and Complications Trial,[5] these findings support good glycemic control with frequent, low doses of insulin to avoid wide swings in both blood glucose and circulating insulin levels.

Angiotensin II

In addition to the direct effects of insulin on collagen, fibronectin, and laminin synthesis, insulin may act in concert with other factors to determine the ultimate amount and composition of ECM expressed by mesangial cells. One factor that has received considerable attention recently is angiotensin II. Studies in humans that demonstrate that the rate of progression of diabetic nephropathy can be slowed by angiotensin-converting enzyme inhibitors have prompted the evaluation of additional actions of angiotensin II. Early studies of mesangial cells in culture showed that angiotensin II–induced contractility required insulin in the medium.[29] More recently it was shown that insulin treatment of mesangial cells increases angiotensin II–receptor expression and increases the sensitivity of angiotensin II–induced stimulation of calcium channel transport.[30] Thus, insulin may augment all angiotensin II–mediated actions on mesangial cells. Angiotensin II stimulates the transcription and protein synthesis of collagen I, but not collagen IV,[31] and it increases the levels of IGF-I, platelet-derived growth factor A, basic fibroblast growth factor, and TGF-β synthesis in vascular smooth muscle cells.[32,33] These last-named stimulatory effects of angiotensin II could lead to continued alterations in the amount and type of matrix proteins that accumulate in diabetic nephropathy, because each of these growth factors has been shown to regulate mesangial cell proliferation and ECM synthesis in vitro.[34,35] For example, we have shown that IGF-I increases collagen I, III, and IV synthesis by mesangial cells,[28] but only in mesangial cells that have had long-term exposure to insulin. These in vitro effects of angiotensin II provide an important rationale for treatment trials in which angiotensin II levels are reduced by the administration of angiotensin-converting enzyme inhibitors.[36]

Summary

Progressive mesangial matrix expansion that leads to end-stage renal disease in patients with diabetic nephropathy develops slowly after many years of exposure to a complex, abnormal metabolic milieu. Many factors undoubtedly interact to produce this lesion (see Figure 1). Evidence from cell culture, animal models, and patients with diabetes mellitus shows that many factors in the diabetic milieu contribute to an increased synthesis and accumulation of ECM proteins normally present in mesangial matrix, as well as the appearance and accumulation of ECM components not normally present. The exposure of mesangial cells to insulin can induce a new expression of collagens I and III with a reduction in the rate of synthesis and the incorporation of collagen IV into the ECM. Glucose-mediated increases in fibronectin synthesis are reduced by insulin treatment, as is the expression of the extra domain A–containing isoform of fibronectin. Insulin increases the synthesis of laminin and thrombospondin and specifically induces a change in the isoform of laminin. Thus, under the influence of insulin, a mesangial matrix of entirely different composition accumulates. Periods of increased intrarenal synthesis of angiotensin II likely further stimulate the accumulation of some of these matrix proteins, specifically collagen I and laminin. Exposure to hyperglycemia augments the synthesis of all matrix components, those normally present and newly expressed ones. Together these factors lead to the steady accumulation of mesangial matrix of abnormal composition. During periods of continued abnormalities in glucose, insulin, angiotensin II, and other growth factors, a vicious cycle of increased synthesis of mesangial matrix with altered composition steadily progresses toward the ultimate occlusion of the glomerular capillary loop. Mesangial cells normally synthesize matrix-degrading enzymes that degrade type IV collagen and matrix glycoproteins, but not enzymes that degrade interstitial collagens; thus, they may preferentially accumulate. Abnormal cross-links between ECM proteins that result from nonenzymatic glycosylation may further impair the degradation of these proteins. Additional studies are needed to define the role that matrix-degrading enzymes play in the progressive expansion of mesangial matrix in diabetes mellitus.

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Articles

Atypical and Complicated Kawasaki Disease in Infants

Do We Need Criteria?

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Case reports suggest that infants with Kawasaki disease have atypical presentations and a high complication rate, likely related to delayed diagnosis and treatment. To date, no study of consecutive cases has compared infants with older children who have both atypical and typical Kawasaki disease. We retrospectively reviewed 44 cases of Kawasaki disease treated at our hospital from March 1980 to 1990: 11 (25%) were infants; 9 (20%) had atypical Kawasaki disease, of which 5 (56%) were infants; the male to female ratio was 1.7:1. Infants had a higher incidence of atypical Kawasaki disease (5 [45%] versus 4 [12%]; $P = .007$) and of coronary artery complications (7 [64%] versus 3 [9%]; $P = .002$), and coronary artery complications developed in all of the infants with atypical Kawasaki disease (5 [100%] versus 0 [0%]; $P < .01$). Yet, the other manifestations and laboratory changes were at least as common as in the older children. Coronary artery complications did not develop in any patient who received early intravenous immune globulin therapy. We suggest that in infants with Kawasaki disease, accepted criteria are too restrictive to allow early diagnosis and effective treatment. Until a definitive test is available, clinical judgment is required in the diagnosis of atypical Kawasaki disease. Intravenous immune globulin is known to be safe, and its early use in patients with suspected atypical Kawasaki disease is appropriate.

(Joffe A, Kabani A, Jadavji T: Atypical and complicated Kawasaki disease in infants—Do we need criteria? West J Med 1995; 162:322-327)

Kawasaki disease is not new. It was first described in 1967 in Japan[1] and later in the English-language literature in 1974 by T. Kawasaki, who suggested the name mucocutaneous lymph node syndrome.[2] As early as 1959, however, in a review of 18 cases of infantile periarteritis nodosa, premortem and postmortem findings were noted to be strikingly similar to those of atypical Kawasaki disease.[3] Infantile periarteritis nodosa and mucocutaneous lymph node syndrome have since been shown to be histologically indistinguishable.[4-7] Atypical cases of Kawasaki disease are also histologically indistinguishable from the typical form,[8] and the number of reports of this form of the disease has escalated in recent years.[9]

In a literature review of atypical Kawasaki disease, 23 case reports were found after 1980,[9-22] and more are referenced in Japanese publications. In addition, a review of 45 atypical cases at the Japan Red Cross Medical Center was reported in 1987 (Japan Kawasaki Disease Research Committee, Department of Pediatrics, Japan Red Cross Medical Center, Tokyo). These authors have shown that atypical Kawasaki disease has the same, but probably more frequent, occurrence of coronary artery complications and that it differs in some respects from typical Kawasaki disease. To date, there has not been a study of consecutive cases comparing infants with older children with both atypical and typical Kawasaki disease.

We report a retrospective review of 44 cases of Kawasaki disease seen consecutively at our hospital from 1980 to 1990 and compare the cases of infants with those of older children with both typical and atypical presentations. The study was directed at answering the following questions:

- Do infants differ from older children in manifestations or complications of Kawasaki disease?
- How does atypical Kawasaki disease differ from the typical form?
- Will any difference aid in early diagnosis and therapy?
- Can coronary artery complications and mortality be prevented?

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
IVIG = intravenous immune globulin

Patients and Methods

We reviewed the medical records of all children admitted to our hospital (Alberta Children's Hospital, Calgary) from January 1980 to February 1990 with a discharge diagnosis of Kawasaki disease or mucocutaneous lymph node syndrome. In addition, we reviewed all autopsy and echocardiogram reports from 1980 to 1990 at our hospital for the documentation of coronary artery aneurysm. The diagnosis of Kawasaki disease was accepted if one of the following conditions applied:

- Criteria set by the Centers for Disease Control and Prevention (CDC) were satisfied[23];
- Four of the CDC criteria were present, with the subsequent development of periungual desquamation and illness not explained by known pathogens; or
- At least two criteria were present, followed by the development of coronary artery aneurysm.

Patients who met the last two conditions were diagnosed as having atypical Kawasaki disease. All patients were seen by a pediatrician and, since 1985, by a pediatric infectious disease clinician. All patients also had some combination of viral serologic tests (including adenovirus, measles, Epstein-Barr virus), viral culture, and bacterial cultures of blood, urine, and cerebrospinal fluid.

Coronary artery complications, diagnosed in all cases by echocardiography, included coronary artery aneurysm or coronary artery dilatation. Coronary artery dilatation was defined as an arterial dilatation of greater than 2 mm in children younger than 2 years and greater than 2.5 mm in children older than 2 years.[22] Coronary artery aneurysm was defined as the presence of an arterial dilatation greater than 4 mm.

Other associated manifestations included diarrhea consisting of at least four watery stools per day for at least one day; elevated liver function test values—either an aspartate or an alanine aminotransferase level of greater than 40 IU per liter; and aseptic meningitis—a cerebrospinal fluid leukocyte count of greater than 5×10^6 cells per liter (5 cells per mm^3). Mucositis was considered to occur at three sites: pharynx, tongue, and lips; involvement of any one of these was enough to satisfy the criterion. An infant was defined as being 1 year old and younger.

Although the Fourth Revised Diagnostic Guideline from Japan (Japan Red Cross Medical Center) considers the presence of four criteria with coronary artery aneurysm as typical Kawasaki disease, this would diagnose cases at a stage too late for preventive intravenous immune globulin (IVIG) treatment, and we did not follow this guideline. Peripheral desquamation was not accepted as a criterion for typical Kawasaki disease because this also occurs late in the disease.

Statistical analysis of data was done using χ^2 and unpaired two-tailed Student's t test. Because of the multiple comparisons, significance was accepted at a P value of .01 or less.

Results

During the study period, 47 cases were identified with a discharge diagnosis of Kawasaki disease or mucocutaneous lymph node syndrome. No additional cases were identified on screening of all autopsy and echocardiogram reports. Of the 47 cases identified, 3 were excluded because they did not meet definitions for either typical or atypical Kawasaki disease, leaving 44 for analysis.

The patients ranged in age from 2 months to 9 years, 7 months (median, 25 months). There were 28 boys and 16 girls (male to female ratio, 1.7:1). Atypical Kawasaki disease accounted for 9 cases (20%). Infants accounted for 11 cases of Kawasaki disease (25%), with 5 cases of the atypical form (56%). Of the 5 infants with atypical Kawasaki disease, the cases of 3 (60%) satisfied four criteria, with subsequent periungual desquamation and illness not explained by known pathogens. All cases of atypical Kawasaki disease in infants satisfied at least two criteria, followed by the development of coronary artery aneurysm. Of the 35 patients with typical Kawasaki disease, 26 (74%) were younger than 4 years of age, 24 (68%) were younger than 3 years of age, and 17 (48%) were younger than 2 years of age. Fever was present in all 44 patients (100%).

Infants were found to differ from older children in several respects. Infants had substantially less extensive mucositis, pharyngitis, cervical adenopathy, and conjunctivitis. They also had a higher proportion with no mucositis (4/11 versus 0/33, $P = .01$). These differences were even more pronounced when infants with atypical Kawasaki disease were compared with older children (Table 1). Particularly noteworthy were the absence of cervical lymphadenopathy and the patchy mucosal involvement in infants with atypical Kawasaki disease. The most common findings were rash and fever.

The other manifestations and laboratory changes of Kawasaki disease were at least as pronounced in infants, including those with atypical Kawasaki disease, as in the older children. Infants had a high incidence of diarrhea and irritability, with a trend toward a more prolonged fever ($P = .04$, Table 1). Infants had elevated leukocyte counts, elevated platelet counts, and increased erythrocyte sedimentation rates, with a high incidence of sterile pyuria, elevated liver function test values, and a substantially lower hemoglobin level than older children (Table 1). Thus, despite fewer classic findings in the accepted criteria of Kawasaki disease, infants still had the other manifestations of the disease, including the laboratory changes.

Coronary artery complications were significantly more common in infants—7 (64%) versus 3 (9%) in children older than 1 year ($P = .0002$). This difference was most notable in infants with atypical Kawasaki dis-

TABLE 1.—*Findings of Kawasaki Disease in Infants and in Older Children*

Clinical Features	Kawasaki Disease: Atypical, ≤ 1 yr (n = 5)* No.	(%)	Typical, <1 yr (n = 6)* No.	(%)	All, >1 yr (n = 33)* No.	(%)
Criteria						
Cervical lymphadenopathy	0	(0)	2	(33)	23	(70)†‡
Conjunctivitis	2	(40)	5	(83)	33	(100)†‡
Peripheral edema or erythema	2	(40)	4	(67)	25	(76)
Pharyngitis	2	(40)	2	(33)	27	(82)†
Diaper rash	1	(20)	4	(67)	18	(54)
Other rash	5	(100)	6	(100)	31	(94)
Mucositis ≤1 site	5	(100)	2	(33)	3	(9)†‡
Other symptoms						
Diarrhea	4	(80)	2	(33)	14	(42)
Irritability	5	(100)	5	(83)	24	(73)
Fever, days	15 ± 8.9		11.6 ± 5.7		9.6 ± 3.8	
Hospital days to diagnosis	4.0 ± 3.4		1.7 ± 2.4		1.7 ± 2.3	
Total days to diagnosis	8.8 ± 2.7		9.5 ± 4.0		7.9 ± 3.4	
Laboratory tests						
Leukocyte count, $\times 10^9$/liter	30.5 ± 19		16.4 ± 3		17.5 ± 6	
Hemoglobin, grams/liter	80 ± 24		95 ± 5		104 ± 9†	
ESR, mm/hr	94 ± 13		89 ± 18		85 ± 26	
Platelets, $\times 10^9$/liter	858 ± 326		971 ± 295		733 ± 196	
PMN in differential count, %	67 ± 12		63 ± 15		74 ± 10	
Sterile pyuria	4	(80)	3	(50)	25	(76)
Elevated liver enzymes	3	(60)	2	(33)	14	(42)
Male:female ratio	1.5:1		2:1		1.8:1	

ESR = erythrocyte sedimentation rate, PMN = polymorphonuclear leukocytes

*The number of infants and children affected (with percentages) is given; other values are given as n ± 1 standard deviation.

†$P < .01$ comparing infants ≤ 1 year with children > 1 year.

‡$P < .01$ comparing infants ≤ 1 year with atypical Kawasaki disease with all children > 1 year.

ease, all 5 of whom had coronary artery complications (an incidence of 100%; $P < .01$). Overall, patients with atypical Kawasaki disease had a higher incidence of coronary artery complications—5 (56%) versus 4 (14%) in the typical cases ($P = .001$).

The benefit of IVIG therapy is evident in Table 2. Coronary artery complications did not develop in any patients who received IVIG treatment before echocardiographic evidence of such complications, regardless of age. In those not treated with IVIG, coronary artery complications developed in 7 infants (88%) and 3 children older than 1 year (25%). Coronary artery complications developed in all infants with atypical Kawasaki disease, and the only one in whom an aneurysm did not develop received IVIG therapy when coronary dilatation (diameter, 3.5 to 4 mm) was identified. The only death occurred in a 3-month-old infant who presented with atypical Kawasaki disease. The male to female ratio for coronary artery complications was 1.3:1 for infants; all three of the children older than 1 year who had such complications were boys, and all had a coronary artery aneurysm.

Other findings of note include that desquamation of diaper rash occurred toward the end of the first week, whereas peripheral desquamation occurred toward the end of the second week. Irritability was present in 28 of the 30 children younger than 3 years (93%) and only 6 of the 14 children older than 3 years (43%; $P < .01$). Pneumonitis, diagnosed by evidence on chest x-ray film, occurred in 9 (26%) of the 35 children with typical Kawasaki disease and 2 (22%) of the 9 children with atypical Kawasaki disease. Gallbladder hydrops was found in 2 cases (4%) on ultrasonography. On examination of the cerebrospinal fluid of 7 patients, 6 of whom were infants, 5 with atypical Kawasaki disease, aseptic meningitis was found in 4; all were infants, 3 with atypical Kawasaki disease (60%). A history of recent exposure to rug shampoo was reported in 10 cases (38% of all asked; n = 26).

Discussion

In 1959 Munro-Faure reported that most patients with infantile periarteritis nodosa had at some time during their illness at least six of the following symptoms and signs: fleeting macular skin eruptions, fever, leukocytosis, conjunctivitis, pharyngitis, cervical adenitis, and cough.[6] Other reviews of infantile periarteritis nodosa from 1963 and 1968 also conclude that there is a rather constant clinical syndrome that in retrospect is identical to atypical Kawasaki disease.[24,25] There is also a report of a nonfatal case of infantile periarteritis nodosa in which the diagnosis was based on angiographic evidence of coronary artery aneurysm that fits present-day criteria for atypical Kawasaki disease.[26] Munro-Faure suggested that

> the persistence of these symptoms beyond the usual duration of an upper respiratory infection in an infant whose condition gives cause for concern, should lead to the consideration of necrotizing arteritis. . . . It may well be that early institution of therapy could avoid a fatal outcome.[3(p925)]

Now, 36 years later, therapy with IVIG combined with high-dose salicylate is known to prevent coronary artery complications if given before symptoms

TABLE 2.—*Incidence of Coronary Artery Complications (CAC) With and Without Intravenous Immune Globulin (IVIG) Therapy in Infants and Older Children With Kawasaki Disease*

IVIG Therapy Given Before CAC Noted on Echocardiogram	Age, yr	Patients, No.	With CAC on Follow-up, No.	(%)
Yes	≤ 1	3	0	(0)
	> 1	21	0	(0)
No	≤ 1	8	7	(88)
	> 1	12	3	(25)*

*$P < .01$ using χ^2.

develop.[27-30] It is time to be concerned about the early diagnosis of atypical Kawasaki disease.

The concern of possibly missing the diagnosis of atypical Kawasaki disease in infants has been raised in several case reports.[10-22] Echocardiography has been recommended for various indications: prolonged illness with thrombocytosis,[16] fever lasting more than five days with rash,[14] prolonged fever with subsequent desquamation,[30] prolonged fever with two other criteria,[18] or two criteria with thrombocytosis.[9] The most severe complication of Kawasaki disease is that of the coronary arteries, and if detected on echocardiogram, it should both support the diagnosis and lead to treatment. No evidence exists, however, that treatment with IVIG is effective if initiated after day 10 of illness.[28-31] Thus, by the time coronary artery complications develop—mean time to coronary artery dilatation, day 10[29]—it may be too late for IVIG therapy to be effective. In fact, in our series, coronary artery complications were detected in four of ten patients, including three infants with atypical Kawasaki disease, by day 10 (days 6, 8, 9, and 9, respectively); in another three cases, complications developed on day 11, including in one infant with atypical Kawasaki disease. No coronary artery complications were seen with early IVIG therapy. Thus, a need for echocardiography, although important for diagnosis and follow-up, is inadequate as a criterion for early treatment, and a normal echocardiogram should certainly not preclude treatment.

Several reports have scored infants at higher risk for coronary artery aneurysm.[32,33] The autopsy reviews of infantile periarteritis nodosa[3,4,25] consist mainly of infants (>85%), supporting the view that they have more severe complications. In autopsy cases of Kawasaki disease, 54% are reported to be infants.[5] In our series, the incidence of coronary artery complications was 14% in patients with typical Kawasaki disease, 33% in infants with typical Kawasaki disease, and 100% in infants with atypical Kawasaki disease. Even in patients with typical Kawasaki disease, there have been several attempts at predicting the risk for coronary artery complications.[32-34] A good prediction has been reported with the modified ASAI score, using the single criterion of fever of 14 days or longer. These scores are all based on retrospective criteria, however, and do not aid in either diagnosing atypical Kawasaki disease or predicting the need for IVIG therapy early in the course of the disease. In infants with atypical Kawasaki disease, who are at greater risk for coronary artery complications, predictive scores also are not adequate for early diagnosis and treatment. In the absence of a definitive laboratory test or pathognomonic sign, clinical judgment must be relied on for the early diagnosis of atypical Kawasaki disease.

In this study, infants were compared with older children with Kawasaki disease to look for manifestations that may aid in early diagnosis. Although the number of infants was small—5 with atypical, 6 with typical Kawasaki disease—findings from our series of 44 patients are comparable to information available in the literature (Table 3).[3,4,9-22,35] For typical Kawasaki disease in infants, our results are similar to those of Burns and co-workers,[11] who found an even higher rate of coronary artery complication (71%) and mortality (14%) than in this study; cervical lymphadenopathy was the least common (43%) and rash the most common (100%) manifestation. For atypical Kawasaki disease in infants, our results are comparable to those found with infantile periarteritis nodosa[3,4] and in case reports in the literature of atypical Kawasaki disease[9-22]; the least common manifestation overall was lymphadenopathy, and the most common were fever and rash. The coronary artery complications rate was high in infants and particularly infants with atypical Kawasaki disease (86% to 100%); it was also high in atypical cases (90% in case reports and 56% in this series) relative to typical Kawasaki disease (20% in literature,[29] and 14% in this series). Most notable was the high mortality in atypical Kawasaki disease (11% to 35%), infants (0% to 14%), and infants with atypical Kawasaki disease (20% to 43%), compared with the generally accepted mortality in typical Kawasaki disease of less than 2%.[29,32,36]

In our study, infants differed substantially from older children in several respects. Infants had fewer of the accepted criteria, including less mucositis, conjunctivitis, cervical adenopathy, and pharyngitis. Infants had a higher incidence of atypical Kawasaki disease (45% versus 12%, $P = .007$) and of coronary artery complications. Still, infants had a high incidence of the other manifestations of the disease, including the laboratory abnormalities. In infants with atypical Kawasaki disease, the same findings applied, with an even higher rate of coronary artery complications (of 100%) and the only death.

Other reports have also found infants to have a high incidence of the various manifestations suggested here as important in early diagnosis. Burns and associates report the cases of infants having pyuria (75%), aseptic meningitis (43%), respiratory signs (75%), and desquamation (75%), with increased erythrocyte sedimentation rates, thrombocytosis, leukocytosis, and anemia[11]; they conclude that infants have an increased risk of coronary artery aneurysm and an atypical evolution of the disease. In a review of atypical Kawasaki disease, the authors comment on irritability (64%), diarrhea (29%), pyuria (44%), respiratory symptoms (47%), aseptic meningitis (75%), elevated aminotransferase levels (18%), and electrocardiographic changes (53%).[9] The series on infantile periarteritis nodosa[3,4,24,25] also refer to cough (50%), abnormal urinary findings (75%), and abnormal central nervous system signs including aseptic meningitis, abnormal electrocardiograms, leukocytosis (87%), anemia (70%), and diarrhea (65%).

We recognize that our study definitions may have created a bias for patients with atypical Kawasaki disease to have a high incidence of coronary artery complications. This high incidence (100%) in infants with atypical Kawasaki disease is not easily explained by this potential bias, however. The conditions defined for atyp-

TABLE 3.—*Literature Data on Kawasaki Disease (KD)*

	Children With Atypical KD			Infants With Typical KD		Infants With Atypical KD			
Clinical Features	*Literature Case Reparts, n = 20*†*	*Sonabe and Kawasoki, n = 45‡*	*This Series n = 9*	*Burns et al, n = 7§*	*This Series n = 6*	*IPN Review, 1959, n = 6‖*	*IPN Review 1977, n = 11¶*	*Literature Case Reports, n = 14**	*This Series n = 5*
Fever ≥5days, %	90	73	89	86	100	83	91	93	100
Mucositis,%	50	76	78	100	100	67	18	36	60
Rash, %	55	40	100	100	100	100	81	72	100
Cervical nodes ≥1.5 cm, %	20	36	0	43	33	33	18	7.1	0
Peripheral extremity edema or erythema, %	15	80#	33	86	66	17	18	21	40
Conjunctivitis, %	45	78	55	86	83	67	36	43	40
≥3 Criteria, %	75	20	22	NA	NA	33	73	79	40
CAC, %	90	21**	56	71	33	100	100	86	100
Age, mo									
Mean	26	26	18.2±15.7	2.6	8.8	6.7	6.5	5.3	6.8
Median	7	NA	11	2	10	6	6	4.5	8
Male:female ratio	1:1	1.14:1	2.3:1	1.3:1	2:1	1.5:1	4.5:1	1:1	1.5:1
Age <1 year, %	70	<50	56	--	--	--	--	--	--
Mortality, %	35	NA	11	14	0	100	100	43	20

CAC = coronary artery complications, IPN = infantile periarteritis nodosa, NA = not available

*From Levy and Koren[9]; Ammerman et al[10]; Burns et al[11]; Canter et al[12]; Cloney et al[13]; Friedman[14]; Fukushige et al[15]; Reller et al[16]; Rowley et al[17]; Schuh et al[18]; Avner et al[19]; Kleiman and Passo[20]; Krapf et al[21]; and Sonobe and Kawasaki.[22]

†Of the 23 case reports in the literature, 3 were excluded, 2 (Ammerman et al[10]; Cloney et al[13]) because they satisfied 5 criteria and 1 (Levy and Koren[9]) because the diagnosis was based solely on "late-stage arteritic changes" in the renal, coronary, mesenteric, and meningeal arteries.

‡From Sonobe and Kawasaki.[22] In their series, atypical Kawasaki disease was defined as "3 or 4 of principal symptoms" with no clinical and laboratory evidence of any other disease known to mimic Kawasaki disease.

§From Burns et al.[11]

‖From Munro-Faure.[3]

¶From Landing and Larson.[4]

#Includes desquamation as a peripheral extremity change.

**In Tada et al,[35] the percentage was 40%. In their series with ≤3 criteria, there was a 33% incidence of coronary artery complications.

ical Kawasaki disease were the same in infants and older children, yet none of the older children with atypical Kawasaki disease had coronary artery complications. In addition, three infants with atypical Kawasaki disease also met the definition of having four criteria with subsequent desquamation. The literature also supports the finding of high complication and mortality rates in these infants (Table 3). Finally, the purpose of our study was to identify findings in these patients, regardless of selection bias, that might be used to allow early diagnosis and treatment, thus preventing cardiac complications. Our findings may indeed apply only to more severely affected patients with atypical Kawasaki disease; however, this is the most important group to address.

With the small numbers, our results should be interpreted with some caution. Still, review of the literature (Table 3) elicited similar findings. Most important are the findings for atypical Kawasaki disease, because infants with typical Kawasaki disease do not pose as great a diagnostic dilemma as infants with atypical disease. Although prolonged fever, rash, and desquamation were common in patients with atypical Kawasaki disease, less reliance on other accepted criteria is appropriate for early diagnosis and treatment. More emphasis should be placed on such manifestations as irritability, diarrhea, hydrocele, and abnormal laboratory data (including leukocyte count, hemoglobin level, platelet count, erythrocyte sedimentation rate, sterile pyuria, liver function test values, and aseptic meningitis). We suggest that in infants with Kawasaki disease, accepted criteria are too restrictive to allow early diagnosis and effective treatment. Until a definitive test is available, clinical judgment is required in the diagnosis of atypical Kawasaki disease. Intravenous immune globulin and high-dose salicylate therapy are known to be safe,[27,28,37] and their early use in suspected cases of atypical Kawasaki disease is appropriate.

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Articles

Pregnant Teens in Prison
Prevalence, Management, and Consequences

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A version of this article was presented at the Western Society for Pediatric Research in Carmel, California, February 20, 1993.

To estimate the number of pregnant and parenting teens currently incarcerated and to assess the correctional health care and social services provided to this target population, we surveyed 430 juvenile detention and long-term correctional facilities in the United States that incarcerate adolescent girls. Of these, 261 (61%) institutions responded and are included in the analysis. Of these facilities, 68% estimated that they were holding 1 to 5 pregnant adolescents on a given day, with a reported yearly (September 1991 to September 1992) census of 2,000 pregnant teenagers and 1,200 teenaged mothers. Nearly half of the facilities (45%) continue to incarcerate after it is determined that a youth is pregnant. Of those institutions that incarcerate pregnant adolescents, 31% provide no prenatal services and 70% provide no parenting classes. Of these facilities, 60% reported at least 1 obstetric complication in their pregnant population. A substantial number of pregnant and parenting adolescents are in custody in the United States. General community standards of health and social services for pregnant and parenting teenagers are not being met by the institutions that incarcerate them.

(Breuner CC, Farrow JA: Pregnant teens in prison—Prevalence, management, and consequences. West J Med 1995; 162:328-330)

A growing number of children and adolescents are arrested each year in the United States. In 1990, almost 2 million youths were arrested; 12%, or 240,000, were female, an increase of 24% since 1986.[1] In 1989, the daily census of female adolescents in custody was 6,700.[2] Most are detained for status offenses such as running away and breaking curfew; yet, 18% were held for delinquent offenses, acts that would be crimes if committed by adults, including murder, theft, and drug or alcohol offenses.[3] Concurrently, approximately 1 million teenagers become pregnant each year, or 1 of 10 of teenaged girls.[4] As more adolescent girls are being arrested, convicted of crimes, and sentenced to long-term correction, the inevitable occurs: pregnant adolescents are incarcerated. If the rates for arrest and incarceration are the same for pregnant and nonpregnant teenagers, we can estimate that at least 24,000 pregnant adolescents are arrested each year or that 670 pregnant teenagers are being incarcerated on a given day. Apart from estimates such as these, the incidence of pregnancy in adolescents who are arrested and ultimately incarcerated is not known. No information is available on the number of teenaged mothers who are currently in custody.

Research on adolescent pregnancy in the past ten years has indicated that multidisciplinary interventions and good prenatal care can improve the outcomes of pregnancy, postpartum attachment, and the future prevention of unwanted pregnancies.[5-11] Juvenile delinquents who are pregnant and incarcerated may be at higher risk for poor outcomes, both medically and socially[12,13]; yet, there has been no systematic review of the basic medical and social services that they receive or the outcomes of their pregnancies.

The purposes of our national study were to estimate the daily and yearly census of pregnant incarcerated adolescents, the yearly census of incarcerated teenaged mothers, and the number of facilities that provide obstetric and social services to their incarcerated pregnant and parenting adolescents. Our conceptual framework was that the number of pregnant teens in institutions is higher than in the general community, that their pregnancy-related care is poor, and that the juvenile corrections system is ill-equipped to serve the special needs of these young women.

Methods

We sent survey questionnaires to representatives from all 430 institutions that incarcerate female adolescents (aged 13 to 18 years) in the United States using information from the National Commission on Correctional Health Care and the Juvenile Detention Directory.[14] Of these, 353 were detention facilities

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TABLE 1.—*Race and Ethnic Breakdown of Total Number (%) Versus Number (%) of Pregnant Incarcerated Teens*

Race/Ethnicity	Total Female Population, No.	(%)*	Total Pregnant Population, No.	(%)
White	105	(51)	689	(36)
African American	62	(30)	891	(47)
Hispanic	17	(8)	243	(13)
Other	24	(11)	91	(4)
Total	208	(100)	1,914	(100)

*From the American Correctional Association.[15]

(shorter than 90-day stays), and 77 were long-term correctional institutions that incarcerate youths for at least six months.

The questionnaire consisted of 19 questions: the demographics of each institution including location, total number of youths in the facility, and occupation of the respondent; estimates of the number of pregnant and parenting teenagers currently in custody or during the previous 12 months (response choices were 0, 1 to 5, 6 to 10, 11 to 25, and more than 25); information on the availability of prenatal health care; policy concerning the return of adolescents to custody after giving birth; data pertaining to the placement of a newborn infant or child while the mother is in custody; a retrospective review of the presence or absence of specific obstetric complications; and an open-ended comment section. Mean and frequency distributions were analyzed using the Statistical Program for the Social Sciences.

Results

A total of 430 superintendents of institutions were sent surveys with instructions to have a health care professional or other qualified person respond. The responses numbered 261, for a response rate of 61%, representing a sample from 41 states. The median number of youths in custody per institution was 30; 49% reported 29 or fewer youths. On the day of the survey, 21% of the respondents reported an average of 0 pregnant teenagers in custody, 68% of the respondents held an average of 1 to 5 pregnant adolescents, 4% incarcerated between 6 and 10 pregnant teenagers, and 1% held 11 to 25 pregnant adolescents in custody.

There were proportionately more African-American adolescent girls who were incarcerated and pregnant than in the overall population of incarcerated female adolescents (Table 1).[15]

Many of the institutions (125 of 231, 55%) release a young woman from custody if she has a confirmed pregnancy. Early releases may occur for one of three reasons: a previous legal action against the corrections center for poor obstetric care; a perception, real or imagined, that these young women may be more likely to stay out of trouble if they are pregnant; or the personnel of the institution indicating that they could not handle the medical or social needs of these young women. Nearly a third of the institutions (30%) have group homes available for court-approved placement after release; the disposition of the other young women is unknown.

Of the responding facilities that retain pregnant youths (106 of 231, 45%), 27% have no social work services available, 31% have no nursing or basic prenatal care, 38% have no obstetric prenatal services, 62% have no nutritionist available, 70% do not teach parenting, and 87% do not provide childbirth education classes. Of those institutions, 78% who retain custody of pregnant teenagers may return them to the custodial facility after delivery. Of the facilities with incarcerated teenaged mothers, 46% had no mother-infant visitation policy in effect. Regarding the temporary placement of children of incarcerated mothers, 29% of the respondents did not know where the children had been placed. Of the respondents who were aware of a child's placement, 64% reported that the children were placed with a family member, 43% were in foster care, and 11% were adopted, some by a family member. When obstetric complication rates were analyzed, 60% of the facilities with pregnant youths in custody reported at least one complication.

Discussion

An extensive review of the literature suggests that ours is the first attempt to count the number of pregnant and parenting adolescent girls from all secure institutions and to review the services provided. If we extrapolate from the daily and yearly estimates, we can project a daily census of at least 500 to 1,000 in the United States. Using the same projection, between 1,800 and 2,500 pregnant adolescents and minimally 500 to 1,000 teenaged mothers were incarcerated from September 1991 to September 1992. These numbers may be an underestimate; many institutions acknowledged that they did not actually know how many adolescent parents were in custody because they do not routinely ask about this when the youths are detained.

From the comment section of the survey, we learned much about the problems each facility faces in dealing with these teens, including only partial use of prenatal and obstetric services available in the public health sector, piecemeal institutional care, and lack of continuity for follow-up care in the community. This may be ascribed to a lack of either funds or knowledge of community resources. We also discovered that a few institutions do provide extensive services for their pregnant and parenting youths and may ultimately serve as models for other correctional institutions. These institutions may have access to university-based adolescent training programs or to departments of public health that are used to dealing with correctional institutions.

The increasing number of pregnant and parenting teens in custody reflects societal changes that are difficult to overlook. Young adolescent women are committing serious violent crimes with or without the knowledge that they are pregnant. It is unknown whether a teen's knowledge of her pregnancy would deter her from continued criminal activity. From the number of teenaged mothers in custody, it would seem, at least for some young women, that it would not. A career in crime

continues for some female delinquents despite pregnancy and parenthood.[16]

How well are we serving these young women and their offspring? Our survey shows that high-risk youths whose use of health care is usually fragmented[13,17] may receive no better care when they are in custody and are more available for services.

Intensive intervention using a multidisciplinary approach with good prenatal care may lead to better results.[5-11] After delivery, a teenaged mother must be thoroughly taught effective parenting skills in the presence of her child to encourage bonding and attachment.[18-20] Adding delinquency and incarceration to the equation mandates the need to intervene and provide appropriate health services. If the basics are not provided, we are endangering these extremely high-risk young women and their children.

When the next survey is done, we recommend that a current breakdown by sex be requested from each institution, rather than the total number of youth; that respondents give an exact number of pregnant and parenting teens in custody rather than estimating a range; and that to improve response rates, telephone follow-up be used for those institutions that had not replied.

Conclusion

Our survey reveals a large number of young women in custody who are pregnant and parenting, with inadequate provision of pregnancy-related services. Further research involving tracking delinquent or incarcerated pregnant and parenting teens is required. The management of pregnant incarcerated adolescents in short- versus long-term facilities should be compared. With all of this information, rational decisions can be made about ways to provide health care services to incarcerated pregnant and parenting youths.

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Conferences and Reviews

Treatment of Nonvalvular Atrial Fibrillation

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Nonvalvular atrial fibrillation is an increasingly common condition. It may cause disabling symptoms and is an important risk factor for stroke. The goals of treatment include the relief and prevention of rate- and rhythm-related symptoms and the prevention of stroke and systemic emboli. Three principal treatments should be considered: pharmacologic rate control, cardioversion and antiarrhythmic therapy to restore and maintain sinus rhythm, and prophylactic anticoagulation or antiplatelet therapy to reduce the risk of stroke. The risks and benefits of each of these therapies have been reviewed. Symptoms, if present, can often be managed safely with rate-directed therapy alone. Until issues regarding safety and long-term efficacy are resolved, cardioversion and antiarrhythmic therapy should be limited to those patients whose symptoms cannot otherwise be controlled. The benefits of warfarin anticoagulation for the primary and secondary prevention of stroke in nonvalvular atrial fibrillation have been demonstrated convincingly by several randomized clinical trials. These benefits must be weighed against the real risk of major hemorrhage. For patients at low risk of stroke, the use of aspirin may be an acceptable alternative to warfarin sodium therapy.

(Stettin GD: Treatment of nonvalvular atrial fibrillation. West J Med 1995; 162:331-339)

Atrial fibrillation is a common condition, the prevalence of which increases with advancing age. In the United States, atrial fibrillation affects only 0.05% of people in their 40s, but it increases in prevalence to nearly 9% of persons in their 80s.[1,2] Less prevalent than hypertension or coronary artery disease, atrial fibrillation is about as common as congestive heart failure (Figure 1).

Atrial fibrillation can be debilitating. As I shall discuss, the rhythm disturbance may cause disabling symptoms. In addition, the presence of atrial fibrillation confers an increased risk of stroke, systemic emboli, and death.[1-5] Atrial fibrillation will become more common as our population ages, and knowledge of how to treat this condition will be increasingly important.

Terms

Valvular atrial fibrillation refers to atrial fibrillation occurring in the presence of valvular heart disease, usually rheumatic mitral stenosis. Nonvalvular atrial fibrillation refers to atrial fibrillation in the absence of mitral stenosis or valvular prostheses. With the decline in prevalence of rheumatic heart disease, the relative prevalence of nonvalvular atrial fibrillation has increased markedly. In the United States, nonvalvular atrial fibrillation now accounts for more than 70% of cases of atrial fibrillation.[6]

Atrial fibrillation usually presents in one of three patterns—isolated, paroxysmal, or chronic. Isolated atrial fibrillation refers to atrial fibrillation that is acute, secondary, and "isolated" to another event or illness, such as hyperthyroidism, pneumonia, pulmonary embolism, or a surgical procedure. After the underlying condition is corrected and sinus rhythm restored, this pattern of atrial fibrillation is unlikely to recur. In contrast, paroxysmal atrial fibrillation is characterized by intermittent episodes of atrial fibrillation, unrelated to an acute event or illness. Paroxysmal atrial fibrillation may, but need not, precede the appearance of the third pattern, chronic atrial fibrillation, in which atrial fibrillation is the predominant rhythm.

This review will focus on nonvalvular atrial fibrillation in its paroxysmal and chronic forms. Henceforth, atrial fibrillation will be used generically to refer to nonvalvular atrial fibrillation unless otherwise specified.

Symptoms

Atrial fibrillation may be asymptomatic and is often noted as an incidental finding.[7] Symptoms attributed to atrial fibrillation include palpitations, fatigue, dyspnea, chest discomfort, and lightheadedness. The prevalence of symptoms among patients with atrial fibrillation is unknown; they may be more likely to occur at heart rates greater than 120 beats per minute. Because the symptoms of this condition may be nonspecific, attributing symptoms to atrial fibrillation in patients with concomitant heart or lung disease can be difficult.

The heart rate in patients with atrial fibrillation may exceed 150 beats per minute. Such tachycardia may

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation
SPAF-I, II = first and second Stroke Prevention in Atrial Fibrillation studies

result in palpitations or chest discomfort and can exacerbate angina in patients with underlying coronary artery disease. With the decreased ventricular filling time during diastole, rapid heart rates may result in inadequate cardiac output and increased left atrial pressure. These hemodynamic derangements can cause lightheadedness and precipitate symptoms of congestive heart failure. In addition, the absence of organized atrial contractile activity results in the loss of the "atrial kick"—that is, the contribution of atrial contraction to ventricular filling. In patients with hypertensive heart disease and other conditions causing decreased ventricular compliance, cardiac output may be heavily dependent on the atrial kick, and these patients may have symptoms even at normal heart rates.

Complications

Atrial fibrillation is a well-known risk factor for stroke and systemic emboli.[3,4,8] The rate of stroke in untreated patients with atrial fibrillation is about 5% per year—a rate about five times that of persons without this disorder (Figure 2).[2,9] The percentage of strokes attributable directly to atrial fibrillation increases with

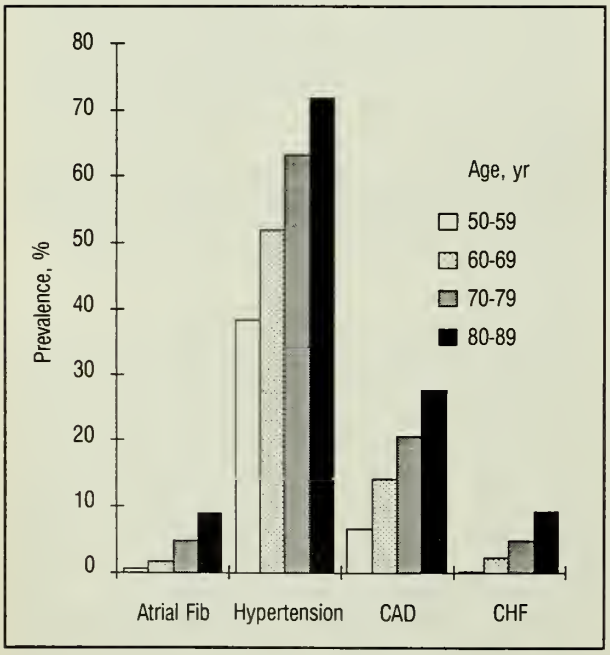

Figure 1.—The prevalence of atrial fibrillation (**Atrial Fib**) increases with advancing age. The prevalences of hypertension, coronary artery disease (**CAD**), and congestive heart failure (**CHF**) are shown for comparision (modified from Wolf et al[2]).

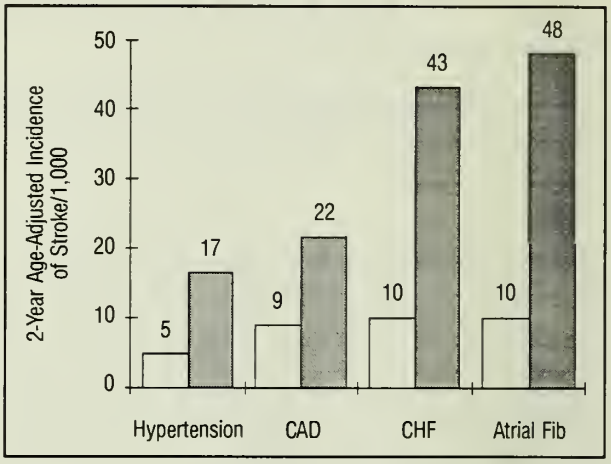

Figure 2.—The 2-year age-adjusted incidence of stroke per 1,000 persons is shown, in the absence (**white bars**) and presence (**shaded bars**) of several cardiovascular conditions: hypertension, coronary artery disease (**CAD**), congestive heart failure (**CHF**), and atrial fibrillation (**Atrial Fib**) (modified from Wolf et al[2]).

age, and in the Framingham [Massachusetts] study, it accounted for nearly a third of all strokes in persons older than 80 years.[2]

Arterial occlusions seen in patients with atrial fibrillation are assumed to be embolic.[5,10-13] Thrombi may develop along the walls of the fibrillating left atrium and then dislodge into the arterial circulation. Resultant emboli may cause stroke or visceral or peripheral ischemia and infarction.

The actual cause of stroke is often difficult to determine, as many patients with atrial fibrillation have concomitant cerebrovascular disease. Studies of the prevalence of thrombotic versus embolic strokes in patients with nonvalvular atrial fibrillation suggest that about two thirds to three quarters of strokes in such patients are embolic in origin.[14,15] Based on these estimates, a similar proportion of strokes in people with atrial fibrillation should be preventable.

With regard to the risk of stroke, "lone atrial fibrillation" deserves special mention because patients with this condition are sometimes thought not to be at increased risk of stroke. Lone atrial fibrillation generally refers to atrial fibrillation in the absence of structural heart disease or concomitant illness. In the Framingham study, persons with lone atrial fibrillation had a fourfold greater risk of stroke compared with those in sinus rhythm.[7] In contrast, patients with lone atrial fibrillation observed at the Mayo Clinic (Rochester, Minnesota) had no increased risk of stroke.[16]

Unfortunately, these two important studies defined lone atrial fibrillation differently, and their conflicting conclusions have led to a great deal of misunderstanding. In the Framingham study, it was defined as atrial fibrillation occurring in adults, in the absence of an acute precipitating factor, coronary artery disease, congestive heart failure, rheumatic heart disease, or hypertensive heart disease.[7] In contrast, Kopecky and colleagues

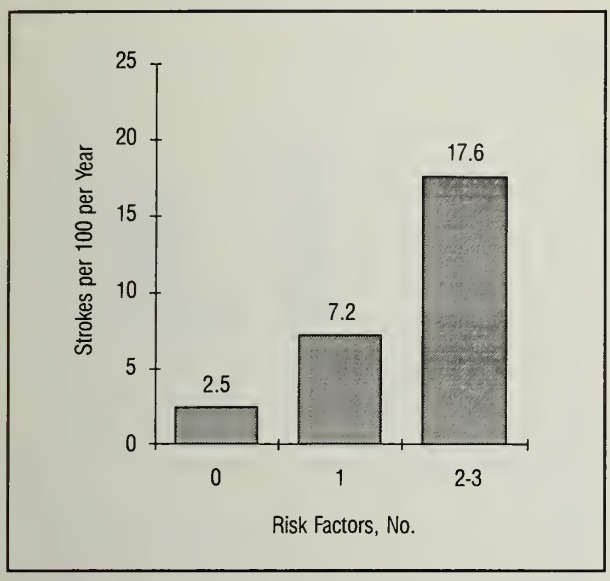

Figure 3.—The rate of stroke in atrial fibrillation increases with the number of major risk factors present. The major risk factors for stroke are hypertension, congestive heart failure, and a history of stroke (modified from the Stroke Prevention in Atrial Fibrillation trial[17]).

defined it more narrowly to include children and persons with isolated atrial fibrillation while excluding those older than 60 years, as well as persons with concomitant hypertension, not just hypertensive heart disease.[16] Further excluded were patients with diabetes mellitus, chronic obstructive pulmonary disease, and any patients who were otherwise "ill." Compared with these persons, those from the Framingham study were much older and had many more comorbid conditions. It is therefore not surprising that Framingham subjects were found to be at increased risk of stroke, whereas young, healthy subjects, without any structural heart disease or even hypertension, were found to do well. To avoid further confusion, "lone atrial fibrillation" is a term that should probably be abandoned.

The risk of stroke among persons with atrial fibrillation was evaluated in the Stroke Prevention in Atrial Fibrillation (SPAF) trial.[17] Hypertension, recent congestive heart failure, and a history of previous stroke were identified as major risk factors for subsequent stroke. The presence of any one risk factor increased the annual rate of stroke from about 2.5% to about 7.2% per year. The presence of any two or three risk factors increased the annual rate of stroke to more than 17% per year (Figure 3). In a separate analysis, subjects with normal left ventricular function and left atrial size as determined by echocardiography, and without any of the aforementioned three major clinical risk factors, had an annual rate of stroke of less than 1%.[18]

Therapy

The goals of therapy in atrial fibrillation are twofold: to alleviate symptoms and to reduce the risk of emboli. The challenge is to meet these goals without causing patients undue harm. This outcome requires an understanding of the risks and benefits of the more commonly applied treatments.

Therapy for atrial fibrillation can be conveniently classified into three categories: rate control, rhythm control, and clot control. Among these categories, some overlap will occur in perceived if not documented benefit. With rate control, we seek to prevent and alleviate rate-related symptoms by maintaining a normal heart rate. The goal of rhythm control is to prevent and eliminate rhythm- and rate-related symptoms by restoring sinus rhythm. Another widely accepted goal of rhythm control is to reduce or eliminate the risk of stroke. Although this goal may make intuitive sense, the prevention of stroke by restoring sinus rhythm has never been demonstrated. The third category of treatment, clot control, is purely preventive. Anticoagulation and antiplatelet drugs are used to prevent embolic events. Patients treated with rate- or rhythm-directed therapies may require concomitant clot control as well.

Rate Control

Rate control aims to prevent and alleviate rate-related symptoms. The three most widely used classes of medication for rate control in atrial fibrillation are digitalis glycosides, calcium antagonists, and β-adrenergic antagonists. These medications effect a slowing of conduction through the atrioventricular (AV) node and thus decrease the ventricular response rate to the fibrillating atria. Most investigators accept a resting heart rate of less than 95 to 100 beats per minute as an adequate response to therapy.

Digoxin, the most commonly used digitalis glycoside, acts directly and indirectly to slow conduction through the AV node. In the absence of renal impairment, the digoxin dosage is titrated to the control of the resting heart rate, short of producing evidence of gastrointestinal or cardiac toxicity. In a monitored setting, digoxin may be given intravenously. When the ventricular response is rapid, as much as 1 mg may be administered in divided doses over a period of several hours. The usual maintenance dosage is less than 0.375 mg per day.

Many investigators consider β-blockers and calcium antagonists, alone or in combination with digoxin, preferable to the use of digoxin alone.[19-21] The inability of digoxin to "control" the ventricular rate during exercise, acute illness, or other high catechol states is well documented.[22,23] Because tachycardia may be physiologic in these situations, the definition of adequate heart rate control is somewhat obscure. Heart rates resulting in symptoms or hypotension, however, are clearly too rapid. In such situations, β-blockers and calcium channel blockers may offer advantages over digoxin. Unfortunately, randomized trials that compare these agents with regard to their effects on symptoms or quality of life in patients with atrial fibrillation are lacking.

In the absence of evidence as to which agent is best, medication for rate control may be chosen based on a strategy of clinical elegance. In patients with concomi-

tant hypertension or coronary artery disease, β-blockers and calcium antagonists may be preferred. The use of β-blockers is probably best avoided in patients with diabetes mellitus or reactive airways disease. Digoxin may be a better choice for patients with poor left ventricular function, but should be used cautiously in patients with renal insufficiency. Fortunately, all three classes of medication have been used widely, and, when used appropriately, they are all safe.

Rhythm Control

The restoration and maintenance of sinus rhythm is thought by many to be the best therapy for patients with atrial fibrillation. The return of sinus rhythm should result in a normal heart rate, improved ventricular filling, and the elimination of rate- and rhythm-related symptoms. Whether the restoration of sinus rhythm is safer or more effective at controlling symptoms than rate control alone remains unknown. In addition, while the restoration of sinus rhythm is thought to reduce the risk of emboli associated with atrial fibrillation, the efficacy of this approach for this purpose has never been shown.

Cardioversion. The restoration of sinus rhythm by electrical or chemical means is known as cardioversion. Reported rates of success for cardioversion vary widely. Comparing different methods and drugs used for cardioversion is nearly impossible, as most of the published studies are uncontrolled case series and their inclusion criteria vary considerably. Patients with atrial fibrillation of recent or remote onset, those with isolated, paroxysmal, or chronic atrial fibrillation, and those with atrial flutter are often considered together, as if these distinct conditions were a single disorder. In fact, new-onset or paroxysmal atrial fibrillation, or both, often reverts to sinus rhythm spontaneously, and atrial flutter responds more readily to cardioversion than does atrial fibrillation. Including patients with these conditions can cause the reported rates of therapeutic success of cardioversion for atrial fibrillation to be overestimated.

Electrical cardioversion: Electrical cardioversion is the most rapid method for restoring sinus rhythm. When cardioversion is indicated emergently, electrical cardioversion is the treatment of choice. Indications for emergency cardioversion include a rapid ventricular response rate with hypotension, pulmonary edema, or evidence of ongoing myocardial ischemia or infarction. For all but the most unstable patients, anesthesia or sedation is used to alleviate the discomfort associated with the procedure. The application of direct-current energy depolarizes the entire heart and allows the return of sinus rhythm. The amount of energy required is generally in the range of 75 to 200 J. Attempts at cardioversion are repeated with increasing levels of energy to a maximum of 360 J, until sinus rhythm is restored or a decision is made to abandon the procedure. This last point deserves emphasis because both patients and physicians should be aware that electrical cardioversion is not always successful. Reported rates of success of 70% to 85% seem reasonable, but may reflect a selection of cases likely to respond.[24,25] The likelihood of achieving sinus rhythm decreases with the duration of atrial fibrillation and increasing age.[25]

Chemical cardioversion: Chemical cardioversion—the administration of antiarrhythmic medication to restore sinus rhythm—is generally an elective or semielective procedure. Although less frequently successful at restoring sinus rhythm than electrical cardioversion, chemical cardioversion precludes the need for anesthesia and sedation. Chemical cardioversion may be applied on an outpatient basis, but the safety of starting a regimen of antiarrhythmic agents in an unmonitored setting remains controversial. Electrical cardioversion remains available as a back-up procedure for patients in whom chemical cardioversion fails.

Digoxin is the only chemical agent that has been studied in a randomized trial of cardioversion. In one study, its use was compared with that of placebo in 36 patients admitted to a hospital with atrial fibrillation of recent onset.[26] Half the patients treated with digoxin had their sinus rhythm restored, as did half the patients treated with placebo. This study provides evidence that, for many patients, the relationship between the administration of medication and the return of sinus rhythm may be coincidental rather than causal.

The two drugs with which we have the greatest experience for chemical cardioversion are procainamide hydrochloride and quinidine. Because it may be given intravenously, procainamide is preferred when the need for cardioversion is semiurgent. Both medications are available in oral form. Quinidine enhances conduction through the AV node, and its use in cardioversion may result, paradoxically, in a more rapid ventricular response until sinus rhythm is restored. For this reason, many investigators recommend pretreatment with digoxin when administering quinidine to patients in atrial fibrillation. Once sinus rhythm returns, there is no evidence that digoxin need be continued.

Risks of cardioversion: Neither electrical nor chemical cardioversion is free of risk. Electrical cardioversion carries with it the risks of anesthesia, sedation, and the induction of ventricular fibrillation. Side effects of chemical agents used in cardioversion include a host of nonspecific symptoms, proarrhythmia, and even death. In addition, cardioversion itself confers an acute risk of stroke and systemic embolism.

Stroke or systemic emboli with electrical cardioversion occurs in about 3% to 5% of persons[24,27] and has been reported to be more likely in patients with previous embolic events, advanced age, coronary heart disease, cardiomyopathy, hypertension, and a long duration of atrial fibrillation.[27,28] Strokes attributed to cardioversion have been reported to occur within hours to weeks following the procedure, possibly because the return of normal atrial contractile activity may lag behind the return of sinus rhythm.[29] Short-term anticoagulation may decrease the risk of embolic events associated with cardioversion. In three separate cohort studies, patients receiving prophylactic anticoagulation with warfarin

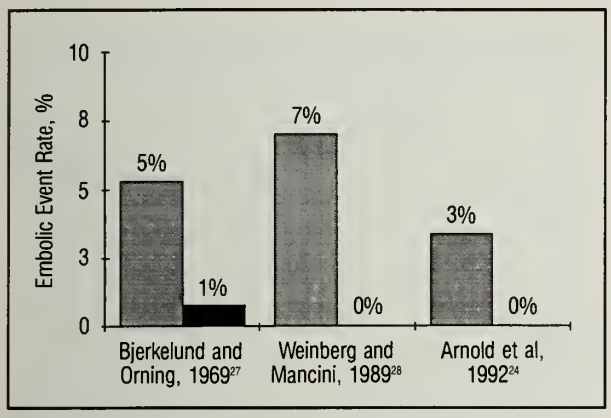

Figure 4.—Cardioversion confers a risk of stroke. Patients not treated with anticoagulation **(shaded bars)** appear to be at higher risk of stroke than those treated with prophylactic anticoagulation **(black bars)**.

sodium were substantially less likely to have embolic events than those not receiving anticoagulation (Figure 4).[24,27,28] In each of these nonrandomized studies, patients with conditions predisposing to embolic events, including valvular heart disease, were more likely to have received anticoagulation, a fact that further strengthens the findings in favor of anticoagulation.

In the absence of contraindications to warfarin therapy, clinicians should anticoagulate all patients undergoing elective cardioversion. Warfarin therapy is started two to four weeks before and continued for another two to six weeks after cardioversion. Because emboli have been seen in persons having been cardioverted from atrial fibrillation of only a few days' duration, the suggestion that patients with atrial fibrillation of recent onset may be cardioverted without anticoagulation appears unfounded.[24] Transesophageal echocardiography may prove useful for excluding left atrial thrombus and identifying patients who can undergo cardioversion safely with a more limited anticoagulation regimen or even no anticoagulation at all. The safety of this approach, however, has yet to be shown adequately. At this time, only patients requiring emergent cardioversion and those patients with clear contraindications to anticoagulation should risk foregoing short-term warfarin anticoagulation.

Maintenance of sinus rhythm. Despite successful cardioversion, atrial fibrillation usually recurs. In the absence of prophylactic antiarrhythmic therapy, the relapse rate is about 75% at one year.[30] Prophylactic antiarrhythmic therapy reduces the rate of relapse substantially, although it remains high. With or without antiarrhythmic therapy, the risk of atrial fibrillation recurring appears to increase directly with age and the duration of the atrial fibrillation before cardioversion.[25,31,32] The influence of left atrial size on the relapse of atrial fibrillation remains controversial.

Choice of prophylactic antiarrhythmic therapy: Even with prophylactic antiarrhythmic therapy, the relapse rate for atrial fibrillation is about 50% at one year.[30,33-35] The effect of quinidine has been studied in the greatest number of patients—more than 400 patients in six separate randomized trials. As summarized in one report, in a meta-analysis of these trials, patients treated with quinidine were twice as likely as those in the control group to remain in sinus rhythm at one year—50% versus 25% (Figure 5).[30] Other controlled studies have shown sotalol hydrochloride to be as effective as quinidine,[33] propafenone hydrochloride to be equivalent to sotalol,[36] and disopyramide phosphate[34] and flecainide acetate[37] to prevent the relapse of atrial fibrillation more effectively than placebo.

Amiodarone deserves special mention because its use in maintaining sinus rhythm after cardioversion is becoming increasingly popular. In a randomized trial involving 54 persons with valvular or nonvalvular atrial fibrillation, the use of amiodarone was found to be more effective than that of quinidine during the first six months after cardioversion.[35] By one year, however, only half of the amiodarone-treated patients and a quarter of the quinidine-treated group remained in sinus rhythm, and this difference was no longer statistically significant. Curiously, the efficacy of quinidine in this trial was only half that observed in the more than 400 quinidine-treated patients in other randomized trials.

Risks of prophylactic antiarrhythmic therapy: All of the antiarrhythmic medications used to treat atrial fibrillation have possible side effects. Gastrointestinal disturbances are particularly common. Even low-dose amiodarone, purported to be well-tolerated, has side effects that, in one study, were "severe" in 4% of patients and "significant" in an additional 13%.[38]

More ominous are the observations that antiarrhythmic therapy for atrial fibrillation may increase a patient's risk of death (Figure 6).[30,39] In a meta-analysis of six randomized trials, Coplen and colleagues found that patients treated with quinidine were more than three times more likely to die than control patients (2.9% versus 0.8%).[30] Although the number of deaths in the quinidine-treated patients compared with control subjects (12

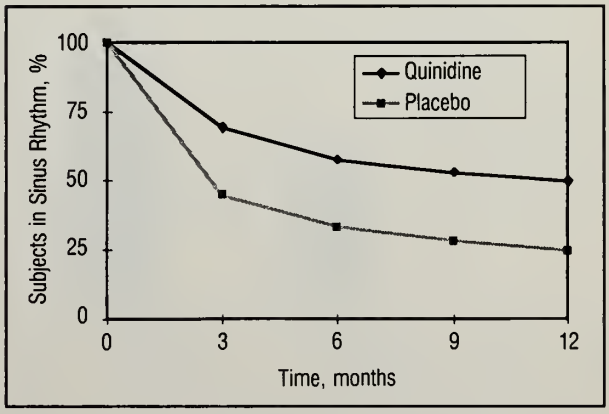

Figure 5.—After cardioversion (time = 0), the percentage of subjects remaining in sinus rhythm falls steadily with time. Antiarrhythmic therapy, here quinidine, prevents the relapse of atrial fibrillation more effectively than placebo (from Coplen et al[30]).

versus 3) may have been statistically significant, the differences in the number of cardiac deaths (6 versus 2) and sudden deaths (3 versus 0) were small and not statistically significant. The cause of death in five of the quinidine-treated subjects was unspecified, however, and these may have been cardiac deaths as well.

The effects of antiarrhythmic medications on mortality were examined in an analysis from the SPAF study, a randomized trial comparing the effects of warfarin, aspirin, and placebo on stroke in patients with atrial fibrillation.[39] Of the 1,330 subjects enrolled in this trial, 220 were treated with antiarrhythmic therapy for atrial fibrillation by their primary physicians. When compared with those with atrial fibrillation not treated with antiarrhythmic medication, a 2.5-fold ($P = .006$) increase in cardiac mortality and a 2.6-fold ($P = .02$) increase in arrhythmic mortality were noted among those taking such medication. Further analysis found this effect most striking in patients with a history of congestive heart failure.

Because the Cardiac Arrhythmia Suppression Trial showed that treatment with the type 1C antiarrhythmic agents encainide hydrochloride and flecainide hydrochloride increased the risk of death in patients after myocardial infarction,[40] observations suggesting similar risks of antiarrhythmic therapy in patients with atrial fibrillation are not totally unexpected. Although the proarrhythmic effects of quinidine, procainamide, disopyramide, propafenone, and sotalol have been well described, long-term evidence of the safety of antiarrhythmic therapy in patients with atrial fibrillation is noticeably lacking. If the findings of Coplen and coworkers are correct, then for every 50 patients treated with quinidine for a year, 1 patient will die prematurely.[30] Before recommending the widespread use of any antiarrhythmic drug, evidence of benefit and safety from randomized trials is needed.

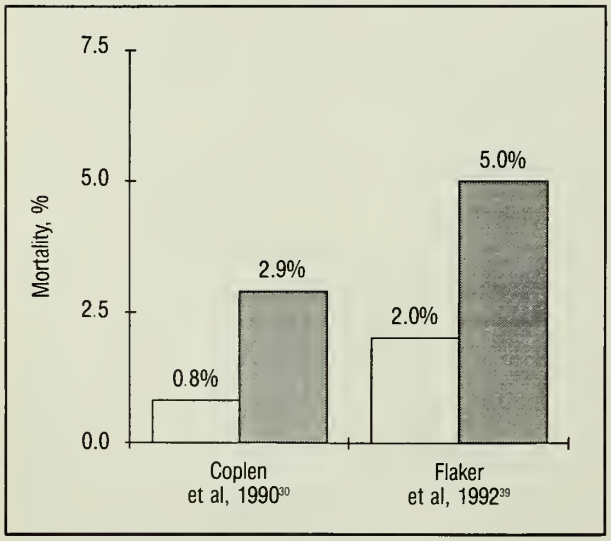

Figure 6.—An increase in mortality has been noted in patients with atrial fibrillation treated with antiarrhythmic therapy (**shaded bars**) when compared with patients receiving no antiarrhythmic medication (**white bars**).

TABLE 1.—*Summary Description of 6 Placebo-Controlled Randomized Trials of Warfarin Sodium Anticoagulation in Nonvalvular Atrial Fibrillation*

Study	*Subjects, No.*	*Age, yr**	*INR†*	*Risk Reduction, %‡*
AFASAK§ (range) ...	1,007	74.2 (38-91)	2.8-4.2	64
BAATAF‖	420	68 (±8.5)	1.5-2.7	86
SPAF-I¶	1,330	67 (21% >76 yr)	2.0-4.5	77
CAFA**	378	68 (±9.3)	2.0-3.0	37
VASPNAF††	538	67 (±7)	1.4-2.8	79
EAFT‡‡	1,221	71 (±7)	2.5-4.0	47

CAFA = Canadian Atrial Fibrillation Anticoagulation, VASPNAF = Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation

*The mean age of subjects at the time of enrollment, with, in parentheses, range, standard deviation, or as specified.

†The international normalized ratio corresponds to the target level of warfarin anticoagulation.

‡Refers to the percentage decrease in risk of major outcome events with warfarin therapy.

§From Petersen et al. AFASAK refers to the Copenhagen study.[44]

‖ From the Boston Area Anticoagulation Trial for Atrial Fibrillation.[42]

¶ From the first Stroke Prevention in Atrial Fibrillation study.[9]

**From Connolly et al.[43]

††From Ezekowitz et al.[41]

‡‡From the European Atrial Fibrillation Trial.[45] This study included subjects with previous stroke or transient ischemic attack.

Clot Control

The third category of therapy in atrial fibrillation is directed at preventing embolic events, particularly stroke. If we can prevent thrombus from forming in the left atrium, we can prevent the embolus. Both warfarin and aspirin therapy have been recommended for this purpose.

Warfarin sodium. The evidence in support of the use of warfarin to prevent stroke in nonvalvular atrial fibrillation is strong. Six randomized trials, together involving more than 4,500 persons with an average age older than 60 years, have shown warfarin to be more effective than placebo.[9,41-45] These studies are described in Table 1.

Intention-to-treat analysis in which, for purposes of analysis, subjects were considered to have received the treatment to which they were initially assigned, biased five of these six studies against finding any benefit with the use of warfarin. Nearly 30% of subjects assigned to receive warfarin withdrew from treatment for an inability to comply with or tolerate the treatment. Despite this handicap, the beneficial effects of warfarin proved profound. These studies were consistent in showing that warfarin therapy greatly reduced the risk of stroke and that this reduction in risk ranged from about 40% to 90%.

For many patients, warfarin may be an inconvenient medication to take. It is a lifelong therapy that must be taken daily. Treatment requires frequent blood monitoring to maintain a safe and therapeutic level of anticoagulation. In addition, patients may need to modify their diets to prevent dietary vitamin K from interfering with treatment.

The most serious concern with warfarin therapy is an increased risk of bleeding, including life-threatening

intracranial and gastrointestinal hemorrhage. The rate of such severe bleeding episodes varied by study, from 0 to 1.6 major bleeding episodes per 100 person-years in control subjects and 0 to 5.8 major bleeding episodes per 100 person-years in warfarin-treated subjects (Figure 7). Fortunately, fatal hemorrhage was rare.

With regard to bleeding, these trials portray a level of safety for warfarin anticoagulation that may be difficult to attain in conventional practice. Study personnel, the "warfarin police," carefully monitored the degree of anticoagulation for each subject. Cases of excess anticoagulation were identified and corrected promptly. The risk of bleeding can probably be reduced by targeting the degree of anticoagulation to the lower therapeutic range, as was done in the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF).[42] In this trial, the warfarin dose was adjusted to maintain a level of anticoagulation corresponding to an international normalized ratio in the range of 1.5 to 2.7.

For patients with nonvalvular atrial fibrillation, the benefits of warfarin therapy in preventing stroke and emboli appear to outweigh the risks of bleeding. Data from the randomized trials indicate that for every 1,000 patients treated with warfarin for a year, 33 to 40 strokes should be prevented at a cost of 1 additional episode of major bleeding and approximately 50 episodes of minor bleeding. Of note, the patients' quality of life, assessed in BAATAF,[47] was not affected by warfarin therapy, except for those patients experiencing major bleeding.

Aspirin. Four randomized trials examined the effect of aspirin use for the prevention of stroke in nonvalvular atrial fibrillation (Table 2). In AFASAK, a Danish study comparing warfarin anticoagulation, low-dose aspirin therapy (75 mg a day), and placebo, the use of aspirin was found to be no more effective than placebo in preventing stroke.[44] Similarly, in the European Atrial Fibrillation Trial, a secondary prevention trial comparing the effects of taking warfarin, aspirin (300 mg a day), or placebo in subjects with nonvalvular atrial fibrillation and a previous episode of transient ischemic attack or minor stroke, aspirin use was not found to be much better than placebo.[45] In the SPAF-I study, a large multicenter American trial comparing the use of warfarin, aspirin (325 mg a day), and placebo, aspirin therapy appeared to be considerably more effective than placebo and nearly as effective as the use of warfarin.[9]

TABLE 2.—*Summary Findings of 4 Randomized Trials Comparing the Use of Warfarin With That of Aspirin in Nonvalvular Atrial Fibrillation*

Study	*Subjects, No.*	*Aspirin Dose, mg/day*	*Event Rates, %**	*Risk Reduction, %†*
Placebo-controlled trials			**Placebo vs aspirin**	
AFASAK‡	1,007	75	5.5 vs 5.5	None
SPAF-I§	1,330	325	6.3 vs 3.6	42
EAFT‖	1,221	300	19 vs 15	17
No placebo			**Warfarin vs aspirin**	
SPAF-II¶	1,100	325	1.9 vs 2.7	NA

NA = not applicable

*Refers to the observed rates of major outcomes (%/yr) with placebo or warfarin therapy versus the use of aspirin.

†The percentage decrease in risk of major outcome events with aspirin use compared with placebo.

‡From Petersen et al.[44]

§From the first Stroke Prevention in Atrial Fibrillation study.[9] Of the 3 placebo-controlled trials, only SPAF-I found a statistically significant reduction in the risk of stroke with aspirin use ($P = .02$).

‖From the European Atrial Fibrillation Trial.[45] The study included subjects with previous stroke or transient ischemic attack.

¶From the second SPAF study.[46] This study compared the use of aspirin with that of warfarin, and the differences in effectiveness were not statistically significant ($P > .05$).

The SPAF-II study, a continuation of the SPAF-I trial, involved 416 SPAF-I subjects initially assigned to take warfarin or aspirin, 265 SPAF-I subjects, most initially assigned to placebo, who were randomly reassigned to take either warfarin or aspirin, and the random assignment of an additional 419 persons.[46] Although fewer ischemic strokes and systemic emboli occurred in patients treated with warfarin compared with aspirin, the overall event rates in both groups were small (1.9% versus 2.7%), and the differences were not statistically significant. Because the rate of embolic events in persons younger than 75 years assigned to aspirin use was so low (1.9%), the marginal benefit of the use of warfarin in such patients seems difficult to justify. For patients thought to be at low risk of embolic events, this study supports treatment with aspirin, as the small benefit of warfarin use is unlikely to outweigh its risk, expense, and inconvenience for such patients.

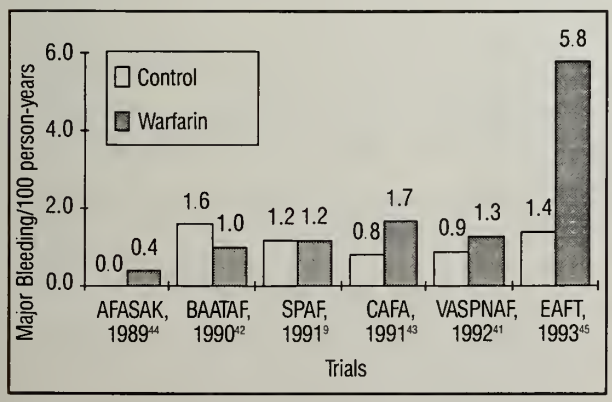

Figure 7.—Therapy with warfarin sodium increases the risk of major bleeding. Data shown are from 6 randomized trials. AFASAK = the Copenhagen study, BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation, CAFA = Canadian Fibrillation Trial, EAFT = European Atrial Fibrillation Trial, SPAF = Stroke Prevention in Atrial Fibrillation, VASPNAF = Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation

Decisions

In caring for patients with nonvalvular atrial fibrillation, consider the goals of therapy from the patients' perspective. Symptoms and the risk of stroke and embolic events must be addressed, and the risks and benefits of alternative treatments should be compared.

Is a patient symptomatic? If so, consider rhythm- and rate-directed therapies. The time-honored dictum that

"every patient deserves a chance at sinus rhythm," however, needs to be challenged. Symptoms and hemodynamic compromise may be relieved with rate control alone. Rate-lowering medications are generally safe and their use well-tolerated. The ability of cardioversion and antiarrhythmic therapy to restore and maintain sinus rhythm is far from perfect, and success is likely to be temporary. Older patients with long-standing atrial fibrillation are particularly unlikely to be maintained in sinus rhythm for long. Theoretically, the restoration of sinus rhythm offers the additional benefit of decreasing or eliminating a patient's risk of stroke and obviates the need for long-term anticoagulation. This theoretical benefit is difficult to justify in light of data suggesting that antiarrhythmic therapy increases mortality. The case against antiarrhythmic therapy is strongest in asymptomatic patients, in patients whose symptoms are relieved with rate-controlling therapy alone, and patients with congestive heart failure, in whom antiarrhythmic therapy appears the most dangerous. For patients in whom unrelenting symptoms necessitate cardioversion, published data support a strategy of short-term anticoagulation unless otherwise contraindicated.

Warfarin therapy is more effective than the use of aspirin or placebo for decreasing the risk of stroke in patients with nonvalvular atrial fibrillation. Reducing the risk of stroke comes at the expense of a small but real risk of major hemorrhage and a larger risk of minor bleeding. In the absence of contraindications to warfarin therapy, the benefits of warfarin use outweigh the risks for those patients at high risk of emboli. The use of aspirin is an attractive alternative to warfarin therapy for certain patients. Its use should be strongly considered for patients unable to take warfarin because of an unacceptably high risk of bleeding or for patients for whom monitoring the degree of anticoagulation is difficult. In addition, aspirin use is appropriate for patients judged to be at a particularly low risk of emboli, even in the absence of treatment. As with any therapeutic decision, the risks and benefits to an individual patient of all available treatment options must be considered before advising that patient on how best to proceed.

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* * *

DON'T HEAR TOO GOOD

Doctors all tell me
I'm quickly going deaf,
that I must learn
to lip-read and sign.
Immediately,
I go out and buy
a grand walnut piano,
bigger woofers and tweeters,
chirping door chimes
and a talking
Pee Wee Herman doll,
a pocket beeper
and cellular car phone,
a honking burglar alarm
and shrieking smoke detector,
a weeping willow,
a whispering palm
and a screaming hyena.
I make sure to move my lips
when I read all the sales contracts
and I sign for everything.

MARAEL JOHNSON©
Del Mar, California

Pituitary Tumors
Current Concepts in Diagnosis and Management

DAVID C. ARON, MD, *Cleveland, Ohio*; J. BLAKE TYRRELL, MD;
and CHARLES B. WILSON, MD, *San Francisco, California*

Diagnostic advances have resulted in earlier and more frequent recognition of pituitary tumors. Pituitary tumors cause problems owing to the hormones they secrete or the effects of an expanding sellar mass—hypopituitarism, visual field abnormalities, and neurologic deficits. Prolactin-secreting tumors (prolactinomas), which cause amenorrhea, galactorrhea, and hypogonadism, constitute the most common type of primary pituitary tumors, followed by growth hormone-secreting tumors, which cause acromegaly, and corticotropin-secreting tumors, which cause Cushing's syndrome. Hypersecretion of thyroid-stimulating hormone, the gonadotropins, or α-subunits is unusual. Nonfunctional tumors currently represent only 10% of all clinically diagnosed pituitary adenomas, and some of these are α-subunit–secreting adenomas. Insights into the pathogenesis and biologic behavior of these usually benign tumors have been gained from genetic studies. We review some of the recent advances and salient features of the diagnosis and management of pituitary tumors, including biochemical and radiologic diagnosis, transsphenoidal surgery, radiation therapy, and medical therapy. Each type of lesion requires a comprehensive but individualized treatment approach, and regardless of the mode of therapy, careful follow-up is essential.

(Aron DC, Tyrrell JB, Wilson CB: Pituitary tumors—Current concepts in diagnosis and management. West J Med 1995; 162:340-352)

The prevalence of pituitary tumors, estimated at 10% to 20% in autopsy series, greatly exceeds the frequency of clinically recognized tumors.[1,2] Advances in biochemical and neuroradiologic diagnosis, however, and improvements in surgical technology have revolutionized the diagnosis and treatment of patients with pituitary tumors.* For example, between 1970 and 1977 a tenfold increase in the incidence of prolactin-secreting tumors coincided with the availability of prolactin radioimmunoassays.[3]

Pituitary tumors are no longer designated as chromophobic, eosinophilic, or basophilic on the basis of histologic appearance. They are now classified according to the hormone(s) they secrete, using immunohistochemical and electron-microscopy techniques (Table 1).

Microadenomas are defined as intrasellar adenomas up to 1 cm in diameter without sellar enlargement or extrasellar extension; macroadenomas are larger than 1 cm in diameter and cause focal or generalized sellar enlargement. The diagnosis of a microadenoma is usually made when there are symptoms or signs of hormonal excess; hypopituitarism is rare, except when caused indirectly, as in decreased growth hormone secretion due to glucocorticoid excess in Cushing's disease. Microadenomas may be incidental findings discovered when a computed tomographic (CT) scan or magnetic resonance (MR) image is obtained for another reason.[1,4] Macroadenomas may also cause manifestations of hormonal excess, but hypopituitarism is common.

Pituitary hormone deficiency tends to begin with growth hormone, followed by the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), and later by thyroid-stimulating hormone (thyrotropin) and corticotropin (adrenocorticotropic hormone). Relatively few patients with macroadenomas have panhypopituitarism at diagnosis, and these patients are not necessarily the ones with the largest tumors. This observation may be accounted for by the fact that hypopituitarism may be produced by interference with the flow of hypothalamic-releasing factors to the pituitary or by destruction of the normal pituitary cells.

The problems caused by pituitary tumors are related to either the hormones they secrete or the effects of an expanding sellar mass. The vast majority are benign; pituitary carcinomas are so rare that they appear only in isolated case reports.[5,6] But pituitary tumors may be invasive without being malignant.[7-9]

*See also the editorial by M. H. Samuels, MD, "Advances in Diagnosing and Managing Pituitary Adenomas," on pages 371-373 of this issue.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
FSH = follicle-stimulating hormone
GH-RH = growth hormone-releasing hormone
Gn-RH = gonadotropin-releasing hormone
IGF = insulin-like growth factor
LH = luteinizing hormone
MR = magnetic resonance
T_4 = thyroxine
TRH = thyrotropin-releasing hormone

Therapy, whether it is surgical resection, irradiation, or drugs, aims to correct the hypersecretion of anterior pituitary hormones, preserve the normal pituitary tissue that secretes other anterior pituitary hormones, and remove or shrink the adenoma itself. In referral centers with the greatest experience, especially surgical experience, these objectives are currently achievable in most patients with microadenomas; however, multiple therapies are frequently required for larger tumors and may be less successful.

Prolactinomas

Prolactin-secreting pituitary adenomas, or prolactinomas, formerly included in the category of chromophobic adenomas, account for about 60% of primary pituitary tumors. Although estrogen has been implicated in the increased frequency of prolactinomas, studies of women taking oral contraceptives have failed to establish such an association.[10,11] Most chromophobic adenomas previously classified as "nonfunctional" actually contain prolactin.[12-14] Prolactinomas vary in size from microadenomas, which most commonly arise from the lateral wings of the anterior pituitary gland, to large invasive tumors with extrasellar extension.[13-17]

Clinical Manifestations

Prolactinomas have different manifestations in men and women. Women commonly present with galactorrhea, amenorrhea, oligomenorrhea with anovulation, or infertility. The amenorrhea is usually secondary and may follow pregnancy or the use of oral contraceptives. The prevalence of hyperprolactinemia is as high as 20% in women with unexplained primary or secondary amenorrhea, even when galactorrhea or other symptoms of pituitary dysfunction are not present. Some of these patients are found to have prolactinomas. In men, excess prolactin secretion produces hypogonadism, but only occasionally causes galactorrhea. Many men experience decreased libido or impotence because serum gonadotropin and testosterone levels are low. Infertility due to a reduced sperm count is a less common initial symptom. Impotence that occurs in patients with hyperprolactinemia may not be reversed by testosterone replacement if hyperprolactinemia is not corrected. Prolactin-secreting microadenomas generally grow slowly, and many show no evidence of progression during years of follow-up.[16,18-20] Among men, prolactinomas frequently go undetected during the initial phase of hyperprolactinemia; therefore, large tumors are more common in men than in women.

A macroadenoma of any type may produce hypogonadism by mechanical damage to the gonadotropin-secreting cells or by interference with the delivery of gonadotropin-releasing hormone (Gn-RH) by the hypophysial-portal system. Hyperprolactinemia itself interferes with the hypothalamic-pituitary-gonadal axis. Prolactin inhibits both the normal pulsatile secretion of LH and FSH and the midcycle LH surge, resulting in anovulation; basal gonadotropin levels are within the "normal" range despite reduced sex steroid levels. The positive feedback effect of estrogen on gonadotropin secretion is also inhibited. Prolactin also affects the ovaries directly. Biochemical estrogen deficiency may be accompanied by symptoms such as decreased vaginal lubrication and osteopenia, as assessed by bone densitometry. Estrogen deficiency also increases the synthesis of adrenal androgens (such as dehydroepiandrosterone sulfate) and may cause hirsutism.

Differential Diagnosis

The extensive differential diagnosis of hyperprolactinemia is shown in Table 2. Pregnancy is one cause. Prolactin secretion increases in pregnancy and may result in serum levels of 200 μg per liter (200 ng per ml) during the third trimester. Hyperprolactinemia persisting for 6 to 12 months or longer after delivery warrants an evaluation

TABLE 1.—*Major Anterior Pituitary Hormones and Their Hypothalamic Regulation*

Pituitary Hormone	*Hypothalamic Factor*	*Effect*
Growth hormone	Growth hormone-releasing factor	+
	Somatostatin	−
Prolactin	Dopamine	−
	Thyrotropin-releasing hormone	+
	Prolactin-inhibitory factor (postulated)	−
	Prolactin-stimulatory factor (postulated)	+
Corticotropin (ACTH)	Corticotropin-releasing factor	+
	Vasoactive intestinal peptide	+
Thyrotropin (TSH)	Thyrotropin-releasing hormone	+
	Somatostatin	−
LH, FSH	Gonadotropin-releasing hormone	+

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, TSH = thyroid-stimulating hormone, + = stimulatory, − = inhibitory

TABLE 2.—*Differential Diagnosis of Hyperprolactinemia*

Physiologic
Pregnancy, lactation
Nonphysiologic
Prolactin-secreting tumors
Prolactinomas—unihormonal
Tumors secreting multiple hormones
Drugs
Dopamine synthesis inhibitors, depletors, and receptor blockers—α-methyldopa, reserpine, verapamil, phenothiazines, thiothixenes, and butyrophenones
Others—estrogen, narcotics
Central nervous system disorders that lead to pituitary disinhibition
Hypothalamic lesions—tumor, sarcoid, histiocytosis X, and other infiltrative diseases
Pituitary stalk lesions—trauma (stalk section) and compression by tumor or other mass lesions
Miscellaneous
Systemic illnesses—cirrhosis, renal failure
Primary hypothyroidism
Chest wall and spinal cord lesions—postsurgical, herpes zoster, burns
Polycystic ovarian disease
Macroprolactinemia
Idiopathic

for prolactinoma. Another cause of hyperprolactinemia is primary hypothyroidism, which may also produce substantial anterior pituitary enlargement, a combination that mimics a prolactin-secreting pituitary tumor.[21] The prolactin response to thyrotropin-releasing hormone (TRH) is usually exaggerated in these patients. A third cause is the ingestion of dopamine depletors or dopamine-receptor blockers such as phenothiazines. Drug ingestion usually results in prolactin levels of less than 100 μg per liter (<100 ng per ml). Other causes include hypothalamic disorders, liver disease, chronic renal failure, polycystic ovarian disease, previous cranial irradiation, breast and chest wall disorders, and spinal cord lesions. Mild to moderate hyperprolactinemia, galactorrhea, and amenorrhea may occur after estrogen therapy or oral contraceptive use, but their persistence is suggestive of prolactinoma. Finally, macroprolactinemia, a disorder characterized by circulating high-molecular-weight forms of prolactin that may be biologically inactive,[22-24] must also be ruled out. When all of these conditions have been excluded, the most likely cause of persisting hyperprolactinemia is prolactinoma, especially if there is associated hypogonadism.[13,14]

The diagnosis of prolactinoma is primarily based on basal prolactin levels and neuroradiologic studies. Although others may disagree, we think that the assessment of the prolactin response to stimulation with TRH or other currently available dynamic tests is not sufficiently sensitive or specific for routine clinical use in distinguishing prolactin-secreting tumors from other causes of hyperprolactinemia.[25-27] Elevated prolactin levels are correlated with tumor size. With few exceptions, basal prolactin levels of greater than 200 μg per liter (>200 ng per ml) are virtually diagnostic of prolactinoma; levels between 100 and 200 μg per liter are usually caused by prolactinoma, usually identifiable on high-resolution MR images as a microadenoma. Diagnosis is much more difficult if the prolactin level is between 20 and 100 μg per liter because this mild to moderate hyperprolactinemia is found in patients with prolactin-secreting microadenomas and many other conditions. Magnetic resonance imaging should

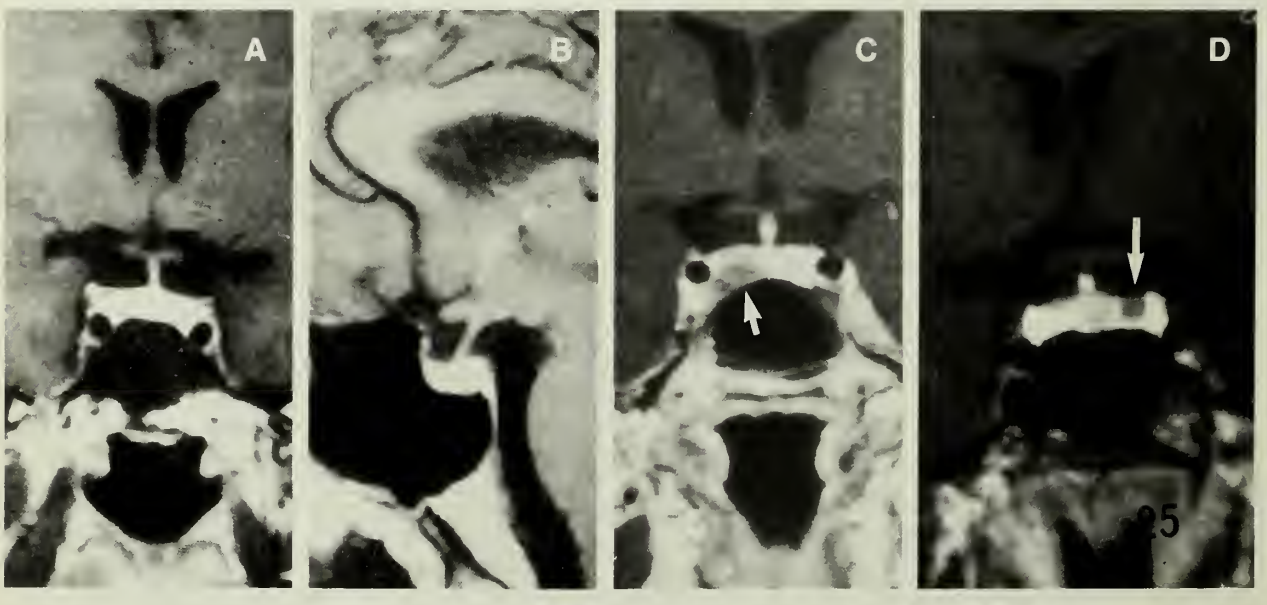

Figure 1.—Gadolinium-enhanced magnetic resonance images are shown of the pituitary gland. **A** and **B**, Coronal and sagittal images show the normal, uniformly enhancing pituitary stalk and pituitary gland. **C**, A pituitary microadenoma appears as a low-intensity lesion in the inferior aspect of the right lobe of the gland (**arrow**). **D**, The pituitary microadenoma appears as a low-intensity lesion between the left lobe of the pituitary and the left cavernous sinus (**arrow**). (Photographs courtesy of David Norman, MD.)

therefore be done in these patients; high-resolution images often show a definite pituitary microadenoma (Figure 1). Computed tomographic scanning is indicated only when MR imaging is not available or its use is contraindicated.[14,28-30] Computed tomographic scans or MR images showing only minor or equivocal abnormalities must be interpreted cautiously because of the high incidence of false-positive results in the normal population.[1] Further evaluation, including serial assessment of prolactin levels, is required to diagnose a prolactinoma. It is important to recognize that hyperprolactinemia associated with pituitary disinhibition related to non–prolactin-secreting sellar and parasellar lesions may mimic a prolactinoma.[31]

Treatment of Microadenomas

The following recommendations apply for patients whose clinical presentation, laboratory data, and MR images have ruled out any reasonable doubt that a prolactinoma exists.

Treatment is recommended to prevent early osteoporosis due to persistent hypogonadism and to restore fertility in all patients with microadenomas.[32-35] Treatment is also recommended for patients in whom neuroradiologic studies show no abnormalities, but who have persistent hyperprolactinemia and hypogonadism, especially if the hypogonadism is of long duration. Prolactin hypersecretion, galactorrhea, and abnormal gonadal function can be satisfactorily controlled in most patients with prolactin-secreting microadenomas. Whether the primary therapy should be medical or surgical is more controversial.[13,36-38]

Surgery. Transsphenoidal microsurgical resection returns prolactin levels to normal, restores normal menses, and stops galactorrhea in 85% to 90% of patients with microadenomas. Success rates are highest in patients with basal prolactin levels of less than 200 μg per liter (<200 ng per ml) and a duration of amenorrhea of less than five years. In these patients, the risk of serious complications is less than 1%, and surgically induced hypopituitarism is rare. Recurrence rates vary considerably in reported series.[38,39] In our experience, more than 72% of patients have had long-term remissions, and 25% have had recurrences five to ten years after surgical therapy.[40]

Pharmacologic agents. Many clinicians would recommend the use of the potent dopamine agonist bromocriptine hydrochloride instead of surgical treatment. It has been used extensively and has effects at both the hypothalamic and pituitary levels.[41,42] The dose is 2.5 to 10 mg per day orally in divided doses. Side effects (dizziness, postural hypotension, and nausea), common early in the course of therapy, usually can be avoided by starting with a low dose and may resolve with continued treatment. Bromocriptine directly inhibits prolactin secretion by the tumor, thereby successfully reducing levels to normal in more than 90% of cases. This allows normal gonadal function to recover and ovulation and fertility to be restored. Hyperprolactinemia usually returns when treatment is discontinued, even after several years, although remissions may occur. Questions remain about possible long-term risks and the indicated duration of therapy for patients with microadenomas.

Bromocriptine restores fertility in most female patients; therefore, mechanical contraception should be advised if pregnancy is not desired. Ovulation should not be induced in patients with hyperprolactinemia without careful assessment of pituitary anatomy and sella turcica size, because pregnancy may cause further expansion of these tumors, although this has been seen in less than 5% of patients.[43] Current data do not indicate an increased risk of multiple pregnancy, abortion, or fetal malformations in pregnancies that occur during bromocriptine therapy; however, it should be discontinued at the first missed menstrual period and a pregnancy test obtained.

Treatment of Macroadenomas

All patients with prolactin-secreting macroadenomas should be treated because of the risks of further tumor expansion, hypopituitarism, and visual impairment. The treatment of women who wish to become pregnant is controversial. Treatment with surgical or radiation therapy before the restoration of ovulation with bromocriptine or gonadotropin therapy will decrease the risk of tumor expansion and visual deficits in the latter part of pregnancy, complications seen in about 15% to 25% in patients with macroadenomas. Therapy with bromocriptine alone may be sufficient, however.[43]

Surgery versus pharmacologic agents. Transsphenoidal microsurgical therapy for macroadenomas is considerably less successful in restoring normal prolactin secretion than it is for microadenomas. If a tumor is 1 to 2 cm in diameter with no extrasellar extension, and basal prolactin levels are under 200 μg per liter, transsphenoidal surgery results in complete tumor resection and restoration of normal basal prolactin secretion in about 80% of cases. In patients with higher basal prolactin levels and larger tumors, the success rate is about 25% to 65%. Although the likelihood of surgical cure is much lower in this group, many centers recommend surgical therapy to decompress vital structures such as the optic chiasm and to reduce tumor bulk and prolactin hypersecretion. Initial treatment with bromocriptine may reduce the tumor size and increase the likelihood of a surgical cure. If surgical therapy is not curative, bromocriptine may be used to control residual hyperprolactinemia. Reported results in general come from centers with the most experience, and it cannot be assumed that these results are easily duplicated.

Many clinicians recommend treatment with bromocriptine instead of transsphenoidal resection[36,37] because it controls hyperprolactinemia in many patients with prolactin-secreting macroadenomas, even when basal prolactin levels are markedly elevated,[36,44] and reduces tumor size within days or weeks in about 70% to 80% of patients (Figure 2). It also has been used to restore vision in patients with major suprasellar extension and chiasmal compression. Questions remain about the appropriate duration of therapy for patients with macroadenomas.[45,46]

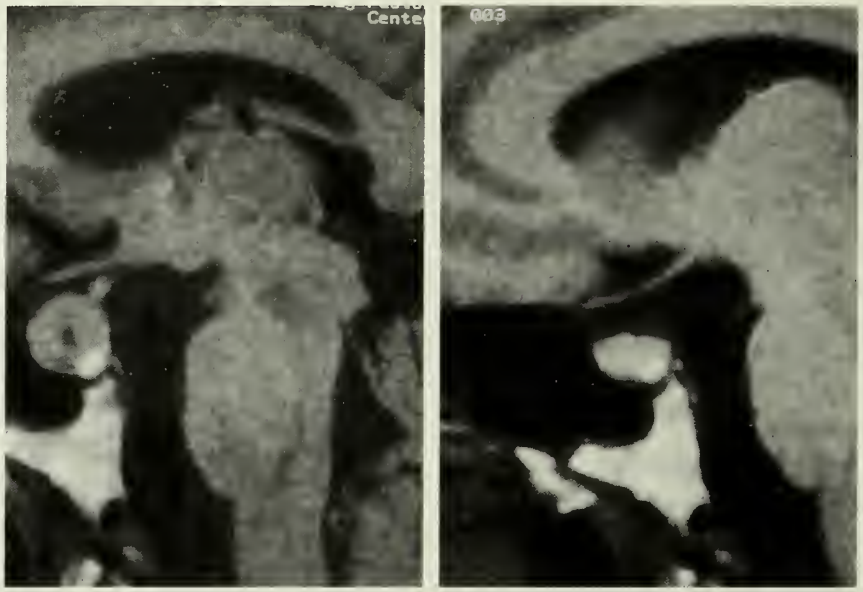

Figure 2.—Sagittal magnetic resonance images were taken of a patient with a prolactinoma treated with bromocriptine hydrochloride. **Left,** The pretreatment image shows a 15-mm adenoma with expansion of the sella turcica and suprasellar extension. **Right,** The post-treatment image after three months of bromocriptine therapy shows pronounced reduction in the size of the adenoma. (Photographs courtesy of David Norman, MD.)

Pergolide mesylate, a newer and more potent agent than bromocriptine, is a long-acting ergot derivative with dopaminergic properties; its use reduces hypersecretion and shrinks most prolactin-secreting macroadenomas.[47] Although this drug has been released, it is not approved for the treatment of hyperprolactinemia. Doses of 25 to 300 μg per day are required to treat hyperprolactinemia. In addition to side effects similar to those of bromocriptine, hepatic and cardiac toxicities have been reported. Other agents are under investigation, including non–ergot-derived compounds.[48]

Radiation therapy. Conventional radiation therapy is reserved for patients with prolactin-secreting macroadenomas who have persisting hyperprolactinemia after surgical treatment and who cannot tolerate bromocriptine. Conventional irradiation to 4,500 cGy prevents further tumor expansion, although prolactin levels rarely fall into the normal range.[44,49] Impairment of anterior pituitary function, a side effect of irradiation, occurs in approximately 30% to 50% of patients.

Treatment of suprasellar extension. A transfrontal craniotomy is required for the 1% to 2% of patients with major suprasellar extension of a macroadenoma requiring decompression of vital structures not accessible by the transsphenoidal route. Bromocriptine or radiation therapy should be given postoperatively because residual tumor is virtually always present.

Growth Hormone-Secreting Pituitary Tumors—Acromegaly and Gigantism

Growth hormone-secreting pituitary adenomas account for about 20% of all primary pituitary tumors.[13] Long-term growth hormone excess has deleterious effects on many systems and results in serious morbidity and a shortened life expectancy, although deaths are rarely due to the space-occupying or destructive effects of the pituitary tumor per se.[50-55]

Growth hormone-secreting pituitary adenomas are responsible for the vast majority of cases of acromegaly,[56,57] the incidence and prevalence of which are estimated to be 50 to 60 cases per million and 3 to 4 cases per million per year, respectively.[50,58] Rates are the same in both sexes.

Pathogenesis

The classic clinical syndromes of acromegaly and gigantism result from chronic growth hormone hypersecretion, which in turn leads to excessive generation of the somatomedins (insulin-like growth factors [IGFs]), the mediators of most of the effects of growth hormone.[59-61] In rare cases, carcinoid or islet cell tumors ectopically secrete growth hormone-releasing hormone (GH-RH), causing acromegaly. More commonly, such tumors express the GH-RH messenger RNA, but do not secrete the hormone itself and, therefore, do not cause the clinical syndrome.[62] Excess levels of ectopic GH-RH due to hypothalamic or pituitary gangliocytomas or hypothalamic hamartoma are extremely rare, and ectopic secretion of growth hormone itself is rarer still.[62]

Growth hormone-secreting pituitary adenomas usually arise from the lateral wings. Because of the slow progression of the clinical manifestations, these tumors are usually greater than 1 cm in diameter when diagnosed; fewer than 10% are diagnosed as microadenomas. Excessive pituitary secretion of growth hormone is a primary pituitary disorder in almost all cases.[56] In acromegaly,

growth hormone is secreted episodically, but the number, duration, and amplitude of secretory episodes are increased, and there is a loss of the characteristic nocturnal surge. Growth hormone dynamics are abnormal, as manifested by a loss of the physiologic suppression of growth hormone levels by glucose. The stimulation of growth hormone secretion by hypoglycemia is absent. Hypothalamic-releasing factors that normally do not stimulate growth hormone secretion (TRH and Gn-RH) may cause its release. Paradoxically, dopamine agonists, which normally stimulate growth hormone secretion, suppress it in about 70% to 80% of cases.[63]

Clinical Manifestations

The clinical features of acromegaly are shown in Table 3. In adults, chronic hypersecretion of growth hormone leads to acromegaly, which is characterized by a local overgrowth of bone, particularly of the skull and mandible. Previous fusion of the long bone epiphyses prevents linear growth. In children and adolescents, chronic growth hormone hypersecretion leads to gigantism[61] because the associated secondary hypogonadism delays epiphysial closure, which allows continued acceleration of linear growth. If growth hormone hypersecretion persists through adolescence and into adulthood, features of acromegaly are superimposed.

Acromegaly is a slowly progressing disorder that is chronically disabling and disfiguring; symptoms usually occur five to ten years before diagnosis. In addition to the classic physical appearance, glucose intolerance and hyperinsulinism resulting from growth hormone-induced insulin resistance are common, occurring in 50% and 70% of patients, respectively. Overt clinical diabetes mellitus is much less common, and diabetic ketoacidosis is rare. Hypogonadism, which is multifactorial in origin, occurs in 60% of female and 46% of male patients; compression of the normal pituitary gland or the pituitary stalk by the tumor may impair gonadotropin secretion directly or by interfering with the delivery of Gn-RH through hypophysial-portal vessels. Associated hyperprolactinemia or the prolactinlike effect of excessive growth hormone secretion may decrease gonadotropin secretion and impair gonadal function. In men, low total plasma testosterone levels may be due to suppression of sex hormone-binding globulin levels by growth hormone; in these cases, plasma free testosterone levels and gonadal function may be normal. Because the diagnosis of growth hormone-secreting adenomas is being made earlier, hypothyroidism and adrenal insufficiency due to destruction of the normal anterior pituitary are unusual, occurring in 13% and 4% of patients, respectively. Galactorrhea occurs in about 15% of patients and is usually caused by hyperprolactinemia resulting from a mixed somatotroph-cell and lactotroph-cell pituitary adenoma. Hyperprolactinemia may also result from lactotroph-cell disinhibition due to stalk compression. Although acromegaly may be a component of multiple endocrine neoplasia type I syndrome, this is seldom the case. For this reason, concomitant parathyroid hyperfunction or pancreatic islet cell tumors are rare.

TABLE 3.—*Clinical Features of Acromegaly*

Disorder	*Signs and Symptoms*
Bony overgrowth	Coarsening of features, frontal bossing, prognathism, malocclusion, barrel chest
Soft tissue swelling	Enlarged hands, feet, and tongue; carpal tunnel syndrome
Skin changes	Increased thickness, skin tags, seborrhea, sweating, hypertrichosis
Degenerative joint disease	
Hyperglycemia	
Hypertension	
Cardiomyopathy	
Fatigue	
Kidney stones	
Manifestations of a pituitary tumor	Headache, visual field defects, hypopituitarism

Complications of chronic hypersecretion of growth hormone include progressive cosmetic deformity and disabling degenerative arthritis and an increased incidence of cancer, especially colonic polyps and colon cancer.[51-57] It has been recommended that patients with acromegaly undergo colonoscopic screening using guidelines similar to those for other high-risk patients such as first-degree relatives of patients with colon cancer.[54] In addition, acromegaly is associated with increased mortality[50,52,58]; the death rate from cardiovascular and cerebrovascular atherosclerosis and respiratory diseases after age 45 in patients with acromegaly is twice that of the healthy population. Death rates are highest in patients with hypertension or clinical diabetes mellitus.

Diagnosis

Acromegaly and gigantism are usually clinically obvious and can be readily confirmed by assessing growth hormone secretion.[63] Basal fasting growth hormone levels (normal, 1 to 5 μg per liter [1 to 5 ng per ml]) are greater than 10 μg per liter in more than 90% of patients and range from 5 to more than 500 μg per liter, with a mean of about 50 μg per liter. Single measurements are not entirely reliable, however, because growth hormone secretion is episodic in acromegaly and because other conditions may increase its secretion, such as anxiety, exercise, acute illness, chronic renal failure, cirrhosis, starvation, protein-calorie malnutrition, anorexia nervosa, and type I (insulin-dependent) diabetes mellitus.

Failure to suppress growth hormone secretion with oral glucose is the simplest and most specific dynamic test for acromegaly. In healthy subjects, the oral administration of 100 grams of glucose suppresses the growth hormone level to less than 5 μg per liter at 60 minutes (<2 μg per liter in most). In patients with acromegaly, growth hormone levels fail to decrease to less than 5 μg per liter,

and this lack of response is diagnostic. Other tests that help establish or confirm the diagnosis are growth hormone stimulation with TRH, the absence of a nocturnal growth hormone surge, and the paradoxical suppression of growth hormone by levodopa, dopamine, bromocriptine, or apomorphine. These tests are usually unnecessary except in patients with mild acromegaly who may have normal or only mildly elevated growth hormone levels and equivocal responses to glucose suppression. Estrogen therapy may increase growth hormone responsiveness to various stimuli, but manifestations of excess should be recognizable. The measurement of somatomedin-C (IGF-I) levels, which are elevated in patients with acromegaly, is another useful diagnostic test for growth hormone hypersecretion and has excellent test characteristics. It is especially useful in differentiating patients with acromegaly from those with diabetes mellitus. Patients with diabetes may have elevated growth hormone levels that are not suppressible with glucose; their somatomedin-C levels are normal or low, however.[63]

Treatment

All patients with acromegaly or gigantism should undergo therapy to halt progression of the disorder and to prevent later complications. The objectives of therapy are to remove or destroy the pituitary tumor, reverse growth hormone hypersecretion, and maintain normal anterior and posterior pituitary functions. These objectives are currently attainable in most patients, especially those with smaller tumors and only moderate growth hormone hypersecretion. In patients with large tumors and pronounced growth hormone hypersecretion, several therapies are usually required to achieve normal secretion. A basal value of less than 5 μg per liter is considered normal by most; more rigorous criteria would be a growth hormone level of less than 2 μg per liter after oral glucose administration and a return to normal of IGF-1 levels. Many patients whose basal values fall in that range, however, do not have normal growth hormone secretion and dynamics.

Surgery. Selective removal of the adenoma by transsphenoidal resection is the therapy of choice. In our experience, transsphenoidal surgical resection successfully reduces growth hormone levels in about 85% of patients and in more than 90% of patients with tumors less than 2 cm in diameter.[64] In patients with larger tumors and basal growth hormone levels greater than 50 μg per liter, particularly those with major extrasellar extension of the adenoma, resection of the adenoma is more difficult, and growth hormone levels are successfully reduced in only 60% to 70%. The recurrence rate after a successful initial response was 5% at our institution.[64] Serious surgical complications or damage to the normal pituitary gland occur in 1% to 2% of patients. Craniotomy is indicated for the rare cases in which major suprasellar extension precludes the transsphenoidal approach.[64,65]

Radiation therapy. Conventional radiation therapy in doses of 4,500 to 5,000 cGy prevents tumor progression and successfully reduces growth hormone hypersecretion in 60% to 80% of patients, although these levels may not return to normal until several years after therapy.[66] In a recent series, growth hormone levels were less than 10 μg per liter in 40% of patients two years after treatment, but were lower than these levels in 60% of patients at five years and in 75% at ten years.[66] Irradiation-induced hypopituitarism is common. Hypothyroidism occurred in 19% of the patients in this series, hypoadrenalism in 38%, and hypogonadism in about 50% to 60%. Because it reduces growth hormone levels so slowly, conventional radiation therapy is reserved for patients whose growth hormone hypersecretion persists after pituitary microsurgery.

Pharmacologic agents. The administration of bromocriptine reduces growth hormone levels in 60% to 80% of patients[67]; however, levels of 10 μg per liter or less are reached by only a few patients. In addition, bromocriptine therapy seldom reduces tumor size and is only suppressive; growth hormone hypersecretion rapidly recurs when treatment is discontinued. Therefore, bromocriptine is used as adjunctive therapy in patients with acromegaly whose growth hormone levels have not been adequately reduced by surgical or radiation therapy.

Octreotide acetate, a long-acting analogue of somatostatin, has been effective in the management of acromegaly.[68-71] Its use reduces growth hormone and IGF-I levels to normal in most patients and, in some, causes notable tumor shrinkage. Effective doses appear to be in the range of 100 to 500 μg, administered subcutaneously three times a day. The need for subcutaneous administration is a major disadvantage because long-term therapy is required. Side effects include abdominal pain, steatorrhea, and cholelithiasis.

Corticotropin-Secreting Pituitary Adenomas—Cushing's Disease

Pathogenesis

Corticotropin hypersecretion by a pituitary adenoma (Cushing's disease) is now recognized as the most common cause of spontaneous hypercortisolism (Cushing's syndrome). It is much more common in women; the ratio of females to males is about 8:1.[72-74] Cushing's disease must be distinguished from the other kinds of adrenocorticosteroid excess, namely, syndromes of ectopic secretion of corticotropin and of corticotropin-releasing hormone, adrenal adenomas, and adrenal carcinomas. Corticotropin-secreting pituitary tumors, which are found to be either basophilic or chromophobic adenomas by routine staining, are almost always benign microadenomas. More than 50% are 5 mm or less in diameter, but they cannot always be histologically confirmed.[75] Corticotropin-secreting tumors are rarely large and invasive.

Diffuse hyperplasia of anterior pituitary corticotroph cells or adenomatous nodular hyperplasia, presumed to result from the hypersecretion of corticotropin-releasing hormone, occurs rarely.

Cushing's disease is considered to be a primary pituitary disorder.[74-76] Virtually all patients with Cushing's dis-

TABLE 4.—*Clinical Features of Cushing's Disease*

Obesity, especially truncal
Facial plethora
Hirsutism, acne, and menstrual disorders
Hypertension
Striae
Bruising
Proximal muscle weakness
Hyperglycemia
Psychiatric symptoms, especially depression
Osteoporosis
Susceptibility to infection
Decreased wound healing
Hyperpigmentation
Edema

ease have corticotropin-secreting pituitary tumors. In addition, selective complete removal of pituitary microadenomas by transsphenoidal microsurgical resection corrects corticotropin hypersecretion and hypercortisolism. After the operation, these patients have temporary but often prolonged corticotropin deficiency with secondary hypoadrenalism. Normal circadian rhythmicity of corticotropin and cortisol, responsiveness of the hypothalamic-pituitary axis to hypoglycemic stress, and low-dose dexamethasone suppressibility of cortisol secretion eventually return. There is, therefore, no evidence for a persisting hypothalamic abnormality in these patients.

Clinical Manifestations

The clinical features of Cushing's disease are shown in Table 4. Cushing's disease causes signs and symptoms of hypercortisolism and adrenal androgen excess that develop over months or years. The weight gain is characterized by a peculiar fat distribution with truncal obesity, round facies (moon face), dorsocervical fat accumulation (buffalo hump), supraclavicular fat pads, and a relative sparing of the extremities. Excessive glucocorticoid action also results in a catabolic state with thin skin, easy bruising, and osteoporosis. Hyperglycemia is common. Adrenal androgen excess produces hirsutism and acne and contributes to amenorrhea. Hypokalemia, edema, and hyperpigmentation are less common in Cushing's disease than in the ectopic corticotropin syndrome.

There are several endocrine abnormalities in Cushing's disease: hypersecretion of corticotropin, with bilateral adrenocortical hyperplasia and hypercortisolism; absent circadian periodicity of corticotropin and cortisol secretion; absent responsiveness of corticotropin and cortisol to stress (hypoglycemia or surgical procedures); abnormal negative feedback of corticotropin secretion by glucocorticoids; and subnormal responsiveness of growth hormone, thyrotropin, and gonadotropins to stimulation.

Diagnosis

The initial step in the diagnosis of a corticotropin-secreting pituitary adenoma is the documentation of endogenous hypercortisolism. This is confirmed by demonstrating the presence of abnormal cortisol suppressibility with low-dose dexamethasone and an increased level of urinary cortisol excretion in a 24-hour urine collection.[77]

A corticotropin-secreting pituitary tumor can be differentiated from other causes of hypercortisolism by measuring basal levels of corticotropin in plasma and by the response to suppression testing with high-dose dexamethasone. Patients with Cushing's disease have normal or slightly elevated corticotropin levels ranging from 9 to 44 pmol per liter (40 to 200 pg per ml; normal, 2 to 11 pmol per liter [10 to 50 pg per ml] by sensitive immunoradiometric assays). Low levels (<2 pmol per liter [<10 pg per ml]) usually indicate an autonomously secreting adrenal tumor, and levels greater than 44 pmol per liter (>200 pg per ml) suggest an ectopic corticotropin-secreting neoplasm. Patients with Cushing's disease are occasionally seen who have similar levels; several corticotropin levels using the highly sensitive immunoradiometric assays and corticotropin-releasing hormone testing may be necessary for an accurate diagnosis. The plasma corticotropin levels associated with pituitary tumors, however, overlap those associated with the ectopic corticotropin syndrome. Administration of low-dose dexamethasone fails to suppress corticotropin secretion and, therefore, glucocorticoid secretion in nearly all patients with Cushing's syndrome, but in some patients, the negative glucocorticoid feedback effect is maintained by corticotropin-secreting pituitary tumors. Thus, administering high-dose dexamethasone will suppress plasma or urinary corticosteroids in most, but not all, patients with Cushing's disease.[77,78]

The rapid, overnight high-dose dexamethasone test is a more reliable and simple way to distinguish corticotropin-secreting pituitary tumors from other forms of endogenous hypercortisolism than is the standard two-day suppression test of Liddle. The Liddle test requires administering 2 mg of dexamethasone every six hours for two days.[79] In the rapid overnight test, 8 mg of dexamethasone is given at 11 PM. The next morning at 8 AM, the plasma cortisol level will be less than 50% of baseline in patients with typical Cushing's disease. The failure of the plasma cortisol level to be suppressed indicates the presence of either the ectopic corticotropin syndrome or an adrenal tumor.

Problems in diagnosis are common, especially in distinguishing Cushing's disease from corticotropin secretion from an occult ectopic source.[72,80,81] Ectopic corticotropin from an occult tumor may be indistinguishable clinically from that due to Cushing's disease. The results of high-dose dexamethasone suppression tests should be cautiously interpreted because they are not entirely specific. Neuroradiologic techniques may not show the microadenomas.[77] High-resolution MR imaging of the sella turcica at best has a sensitivity of 60% and may yield false-positive results. Computed tomographic scanning of the adrenal glands may also be misleading. For example, nodular adrenal hyperplasia due to a corticotropin-secreting pituitary tumor may appear as a solitary adrenal mass

and mimic an adrenal neoplasm.[82,83] Although combining information from all of these laboratory tests and MR images often establishes the diagnosis of Cushing's disease, doing so with certainty requires techniques with better sensitivity and specificity. A few centers have experience with taking blood specimens from the inferior petrosal sinuses and a peripheral vein to document a cephalic gradient of corticotropin. Values from the inferior petrosal sinus should be at least two times the simultaneously determined peripheral value. Bilateral simultaneous petrosal sinus sampling with corticotropin-releasing hormone stimulation of corticotropin release has been reported to have 100% sensitivity and specificity.[84,85] When it can be done with such accuracy, it becomes the diagnostic procedure of choice for most patients.[86] It must be performed by a radiologist skilled in catheterization techniques, and even then, serious complications have occurred.[87] Sampling corticotropin from the petrosal sinus occasionally lateralizes the lesion accurately, thereby assisting a surgeon in locating the tumor. Other tests have been proposed, such as assessing the peripheral blood corticotropin response to corticotropin-releasing hormone, but their role has yet to be established.[77]

Treatment

Surgery. Selective transsphenoidal resection of corticotropin-secreting pituitary adenomas is the treatment of choice because of its efficacy, the rapid clinical response, and low complication rate.[88-92] The tumor, which is characteristically found in the anterior lobe tissue, is removed selectively, leaving the normal gland intact. If the tumor is too small to locate during the operation, total hypophysectomy may be performed in adult patients who are past reproductive age and whose biochemical diagnosis has been confirmed with inferior petrosal sinus sampling of plasma corticotropin levels.

Selective microsurgical therapy successfully corrects hypercortisolism in about 85% to 90% of patients with microadenomas.[88-92] Most patients have transient secondary adrenocortical insufficiency requiring postoperative glucocorticoid support until the hypothalamic-pituitary-adrenal axis recovers, which usually takes 6 to 18 months. Total hypophysectomy is necessary to correct hypercortisolism in about 10% of patients with pituitary adenomas; selective tumor removal is unsuccessful in the remaining 5%. Approximately 10% to 15% of patients with Cushing's disease have pituitary macroadenomas or extrasellar extension of tumor. Transsphenoidal surgical therapy is successful in only about 25% of these patients. Surgical results vary widely among centers.

Before pituitary microsurgery was introduced, bilateral total adrenalectomy was the preferred treatment for Cushing's disease, and it may still be used when other therapies are unsuccessful. Bilateral adrenalectomy, however, has a high complication rate, and patients require lifelong hormone replacement. In addition, the preexisting corticotropin-secreting pituitary adenoma persists and may progress, causing hyperpigmentation and invasive complications (Nelson's syndrome).[72]

Radiation therapy. Conventional irradiation in doses of 4,500 to 5,000 cGy leads to biochemical and clinical improvement in as many as 70% of patients with Cushing's disease, but the response to treatment is delayed, and only about 40% of patients are cured.[93] Adjunctive antiadrenal drug therapy has been used with some success, but the ultimate response to radiation therapy is often unsatisfactory, and prolonged drug therapy is therefore required.

Pharmacologic agents. Drugs that inhibit adrenal cortisol secretion are useful in treating Cushing's disease, often as adjunctive therapy.[94] Ketoconazole, an imidazole derivative used as a broad-spectrum antimycotic agent, inhibits the cytochrome P450 enzymes involved in adrenal steroid biosynthesis. In daily doses of 600 to 1,200 mg, the administration of ketoconazole has been effective in managing mild to moderate Cushing's disease. It is also less expensive than other antiadrenal medications. Hepatotoxicity is common, but may be transient.

Metyrapone, an 11β-hydroxylase inhibitor, and aminoglutethimide, which inhibits the conversion of cholesterol to pregnenolone, are expensive drugs that have both been used to reduce cortisol hypersecretion. Their use results in increased corticotropin levels that may overcome the enzyme inhibition; gastrointestinal side effects may limit their effectiveness, however. Hypercortisolism can be controlled more effectively and with fewer side effects by the combined use of metyrapone and aminoglutethimide. They are usually used while awaiting a response to therapy or when preparing patients for surgical treatment.

The use of the adrenolytic drug mitotane (Lysodren [formerly *o, p'*-DDD]) results in adrenal atrophy predominantly of the zonae fasciculata and reticularis and produces the remission of hypercortisolism in about 80% of patients. Mitotane therapy is limited by the delayed response, which may take weeks or months, and by the frequent side effects, including severe nausea, vomiting, diarrhea, somnolence, and skin rash. Moreover, relapse after therapy is stopped is common.

Pharmacologic inhibition of corticotropin secretion with the use of cyproheptadine, a drug with antiserotonin, antihistamine, and anticholinergic effects, has had limited success. The use of bromocriptine has been reported to be effective in rare cases and should probably be reserved for those few patients who have hyperprolactinemia associated with Cushing's disease.

Nelson's syndrome. Nelson's syndrome, the clinical manifestation of a corticotropin-secreting pituitary adenoma after bilateral adrenalectomy in patients with Cushing's disease, is caused by progression of a preexisting adenoma after the restraint of hypercortisolism on corticotropin secretion and tumor growth has been removed.[72,74] The incidence of Nelson's syndrome after adrenalectomy in patients with Cushing's disease ranges from 10% to 78%, depending on the diagnostic criteria used. Pituitary irradiation before or after adrenalectomy does not prevent the development of this syndrome. Classic Nelson's syndrome with progressive hyperpigmentation and an obvious corticotropin-secreting tumor

develops in about 30% of patients undergoing adrenalectomy for Cushing's disease; about 50% have evidence of a microadenoma without marked progression, and in about 20%, progressive tumor never develops. These tumors are among the most aggressive and rapidly growing of all pituitary tumors.

Patients with Nelson's syndrome present with hyperpigmentation, greatly elevated plasma corticotropin levels (usually greater than 220 pmol per liter [>1,000 pg per ml]) and manifestations of an expanding intrasellar mass lesion. Visual field defects, headache, cavernous sinus invasion with extraocular muscle palsies, and even malignant changes with local or distant metastases may occur. Pituitary apoplexy is a relatively frequent complication.

Pituitary surgery, usually by the transsphenoidal approach, is the initial treatment of Nelson's syndrome, but complete resection of the larger tumors is usually not possible. Conventional radiation therapy alone is satisfactory in a few patients, but it is often given after surgical therapy in patients with extrasellar extension.

Thyrotropin-Secreting Pituitary Adenomas

Although rare, thyrotropin-secreting pituitary adenomas are being diagnosed with increasing frequency.[95-98] In our recent experience, thyrotropin-secreting tumors accounted for 2.8% of pituitary adenomas.[95] There is a modest female predominance; the female to male ratio was 1.7:1 in our series. Moreover, there are sex-dependent differences in the tumor biology; men tend to have larger, more invasive, and more rapidly growing tumors that present later in life. The tumors are found to be chromophobe adenomas by routine staining.

Clinical Manifestations

Patients usually present with thyrotoxicosis, goiter, and elevated serum levels of both thyroid hormones (thyroxine [T_4] and triiodothyronine) and elevated or at least inappropriately nonsuppressed thyrotropin, as measured by highly sensitive assays. The diagnosis may be made based on visual impairment caused by the large size of these tumors, rather than on their endocrine activity. Pituitary thyrotropin hypersecretion that occurs when there is no demonstrable pituitary tumor and that may be due to central thyroid hormone resistance has also been reported to cause hyperthyroidism in a few patients.

Patients with thyrotropin-secreting tumors are often resistant to routine ablative thyroid therapy and require large, often multiple doses of radioactive iodine and several operations to control thyrotoxicosis.

Diagnosis

The routine use of highly sensitive thyrotropin assays to evaluate the presence of thyrotoxicosis is likely to detect more cases of thyrotropin-secreting pituitary adenoma. In patients with thyrotropin-secreting tumors (thyrotroph-cell adenomas), thyrotropin levels have ranged from 1 to more than 400 mU per liter (1 to > 400 μU per ml). The ratio of biologically active to immunologically active thyrotropin may be increased. Thyrotropin responses to dynamic testing are variable.[96,99] The administration of TRH (protirelin) rarely stimulates thyrotropin secretion from these tumors, nor does administering T_4, levodopa, or bromocriptine suppress thyrotropin as it does the thyrotropin hypersecretion caused by primary hypothyroidism. The thyrotropin-secreting pituitary adenomas occasionally co-secrete growth hormone and prolactin; hyperprolactinemia may also result from pituitary disinhibition. More than 80% of thyrotroph-cell adenomas secrete free α-subunit; the ratio of the α-subunit to thyrotropin is usually greater than 1. This helps distinguish thyrotropin-secreting tumors from the syndrome of central resistance to thyroid hormone, in which the ratio of the α-subunit to thyrotropin is less than 1[100] and the sella is normal. The differential diagnosis of a thyrotropin-secreting pituitary adenoma also includes rare cases of primary hypothyroidism in which major reactive thyrotroph-cell hyperplasia, sellar enlargement, and, occasionally, suprasellar extension develop.

Treatment

Transsphenoidal surgical resection of the adenoma is the best initial treatment. If thyrotropin hypersecretion persists, ablative treatment of the thyroid with either radioactive iodide (iodine 131) or surgical intervention is necessary to achieve clinical remission of the thyrotoxic state. Treatment directed at the thyroid gland alone may accelerate growth of the pituitary tumor. The administration of octreotide acetate, a long-acting somatostatin analogue, has been effective in decreasing thyrotropin secretion from these tumors when the drug is given in subcutaneous doses similar to those used for the treatment of acromegaly; it has also been shown to shrink the tumors.[101,102]

Clinically Endocrine-Inactive Pituitary Adenomas

Sensitive techniques for detecting pituitary hormone synthesis and secretion have documented that most pituitary tumors thought to be nonfunctional are, in fact, functional. The term "endocrine-inactive" refers to their clinical behavior and not their capacity for hormone synthesis. These tumors can be classified into several types: null cell, oncocytoma, gonadotropin-secreting, glycopeptide-secreting, and silent corticotropin-secreting.[103] Most of these "nonfunctional" tumors synthesize gonadotropins or their subunits.[104-107] Even null-cell tumors can be induced to produce glycopeptide subunits in vitro. Some adenomas contain secretory granules that show immunohistochemical or electron-microscopic characteristics of corticotropin granules when there is no evidence of Cushing's disease (silent corticotroph-cell adenomas) or of other hormones causing no clinical disorders.

Clinical Manifestations and Diagnosis

Endocrine-inactive tumors are usually large at the time of diagnosis and are therefore associated with neurologic manifestations, typically bitemporal hemianopia and hypopituitarism. The endocrine manifestations usually de-

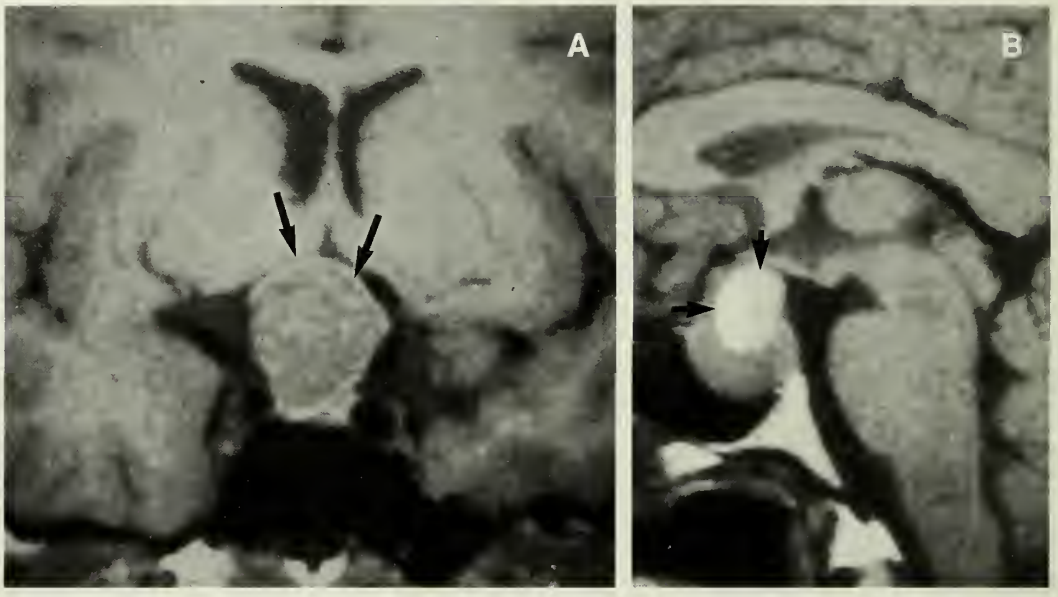

Figure 3.—**A**, The coronal magnetic resonance (MR) image shows a large nonfunctioning pituitary adenoma (arrows) with pronounced suprasellar extension and chiasmal compression. **B**, A sagittal MR image of another large pituitary adenoma shows spontaneous hemorrhage within the suprasellar portion of the adenoma (arrows). (Photographs courtesy of David Norman, MD.)

velop over a period of years. In rare cases, these tumors secrete sufficient amounts of gonadotropins to produce clinical manifestations.[108,109] Until recently, almost all such cases were diagnosed in men. Hypogonadism may be apparent in men or premenopausal women. Some men have testicular enlargement induced by the hypersecretion of FSH, but this is extremely rare. Long-standing primary hypogonadism—such as Klinefelter's syndrome—may cause hyperplasia of gonadotropin cells and pituitary enlargement. This diagnosis must be excluded in any patient with elevated levels of gonadotropins and enlargement of the sella turcica. Serum levels of intact gonadotropins may be normal or slightly elevated. Both α- and β-subunits of the glycoprotein hormones may also be secreted in excess. Pure α-subunit hypersecretion has also been identified. Secretory dynamics of FSH and LH are abnormal, and responses to Gn-RH are variable. The secretion of FSH, LH, and LH-β-subunit, however, is often provoked by TRH; such stimulation is not observed in healthy persons.

Magnetic resonance imaging readily localizes these large tumors (Figure 3). Visual field testing should always be done. Assessing pituitary and end-organ function will determine the presence of hypopituitarism and hypersecretion. Hypersecretion is useful as a tumor marker even if its effects are subclinical. Nonsecreting tumors must be differentiated from nonneoplastic mass lesions.

Treatment

Surgical removal is the initial treatment of choice for endocrine-inactive adenomas. Complete surgical removal is possible in no more than 40% of patients. Postoperative irradiation (4,500 cGy) will obliterate residual cells in almost all incompletely removed tumors and is indicated in most patients when removal is known to be incomplete. There is virtually no role for medical therapy at this time.

Hypopituitarism due to these endocrine-inactive pituitary adenomas, as well as to other macroadenomas, may be reversible if the tumor is surgically removed.[110] In the absence of an endocrine marker of tumor hypersecretion, serial CT scans or MR images and visual field examinations at yearly intervals are required to assess the response to therapy and to detect possible recurrences.

Follow-up After Treatment

Regardless of the mode of therapy, careful follow-up of all patients with pituitary tumors is essential. Patients undergoing transsphenoidal microsurgical resection should be reexamined four to six weeks after the operation to document that the adenoma has been completely removed and that the endocrine hypersecretion has been corrected. Those with successful responses should be examined yearly to look for any recurrence; late hypopituitarism does not occur after the microsurgical procedure. Follow up of patients treated by pituitary irradiation is equally important because the response to therapy may be delayed, and the incidence of hypopituitarism increases with time. At least yearly endocrinologic assessment of both the hypersecreted hormone and the other pituitary hormones is recommended.

Future Research

Research on the pituitary gland continues to yield interesting findings. For example, rare cases have been described of pituitary tumors secreting other hormones such as β-endorphin and cholecystokinin.[111] With the identification of novel hormones in the anterior and posterior pituitary glands and the application of new imaging techniques such as positron-emission tomographic scanning, it is likely that new syndromes will be described in the future.

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Epitomes

Important Advances in Clinical Medicine

Pediatrics

Susan B. Conley, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under the direction of Susan B. Conley, MD, and the panel.

New Antiepileptic Drugs for the Treatment of Childhood Epilepsies

THE GOAL OF THE pharmacologic treatment of childhood epilepsy is to reduce seizure activity and avoid drug toxicity. Meeting this goal has been a challenge because many of the current drugs have potentially serious adverse effects associated with their use, such as bone marrow suppression, liver toxicity, and decline in cognitive function. Therefore, there is a pressing need for new drugs that are effective and safe for use in children.

For the first time since 1978, new antiepileptic drugs have been approved by the US Food and Drug Administration for the treatment of seizures. Although there are several established drugs for treating epilepsies, about 25% of all patients are refractory to medical treatment. New medications are therefore needed for these patients.

Felbamate, introduced in 1993, is the first of the new generation of antiepilepsy drugs to be used in the treatment of childhood epilepsies. It is mainly effective in patients with partial seizures. It is also used to reduce seizure activity in children with the Lennox-Gastaut syndrome—a severe childhood encephalopathy associated with intractable seizures of several types. During experimental trials, this drug was found to be well-tolerated and safe. Common side effects include loss of appetite, weight loss, and insomnia. During the first year of use after its introduction, however, several cases of aplastic anemia and acute hepatic failure have emerged. Because of these serious problems, the use of felbamate is limited to children with severe seizures in whom alternative medications are not effective.

Gabapentin has also been approved for use in the United States in the past two years. It was designed as an analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), but the drug has no effect on the brain GABA system, and the mechanism of its action is unknown. The medication is to be used as an add-on agent in the treatment of refractory partial-onset seizures. Interestingly, this drug is not protein-bound, does not interact with other drugs, and is excreted entirely by the kidneys without undergoing metabolism. It has been approved for use in children older than 12 years. The experience with younger children is limited.

Lamotrigine is a novel drug that appears to be effective for a wide range of seizure types. Its mechanism of action may be related to blocking of the sodium channel and inhibiting the release of the excitatory amino acid glutamate. In children, it appears to be particularly effective for partial seizures, generalized tonic-clonic seizures, absence seizures, and atonic seizures seen in patients with the Lennox-Gastaut syndrome. It has been used by about 80,000 patients in Europe and other countries, and its use is well tolerated by children. Lamotrigine has recently been approved in the United States for use in adults with epilepsy. Dizziness, blurred vision, and ataxia are the most frequent side effects. Rash is the most common side effect leading to discontinuation and occurs particularly frequently when the drug is given with valproic acid. Lamotrigine interacts substantially but predictably with other drugs.

Vigabatrin is another novel agent that appears promising as therapy for children with a wide range of seizure types. Vigabatrin increases brain GABA levels by irreversibly inactivating GABA aminotransferase, an enzyme that breaks down GABA. The drug has been used extensively in Europe and Canada for its apparent effectiveness against infantile spasms, the Lennox-Gastaut syndrome, and partial seizures. In 1983 US clinical trials came to an abrupt halt because this medication caused microvacuolization of the white matter in animals. This has not occurred in humans with exposure to the drug, however, and studies have resumed. Somnolence is the most frequent side effect. Overall, its use is well tolerated, although psychotic symptoms can occur rarely in adults.

Recent advances in antiepileptic drug development hold the promise of substantial improvement in the treat-

ment of childhood epilepsies. Of all the new drugs, lamotrigine and vigabatrin hold the most promise. They have a broad spectrum of efficacy, and their use is well tolerated. They appear to be particularly useful in severe childhood epileptic syndromes. These two drugs should be available soon in the United States for use in children. Considering our inexperience with and possible toxicity of these agents, neurologic consultation is suggested.

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New Drugs for Cystic Fibrosis Lung Disease

SINCE THE DISCOVERY of the molecular basis for cystic fibrosis with the cloning of the gene in 1989, there has been an explosion of new information on the pathogenesis of the disease. Concomitantly, the development of new therapies based on a better understanding of the pathophysiology of the progressive obstructive airways disease that characterizes the pulmonary component has resulted in rapid, revolutionary changes in management that presage the transformation of this lethal disease into a manageable chronic illness.

The approximate cause of the progressive loss of lung function and, ultimately, the respiratory failure that causes death in more than 95% of patients is a relentless, chronic neutrophilic endobronchitis, usually accompanied by chronic infection with mucoid forms of *Pseudomonas aeruginosa*. Recent studies using bronchoalveolar lavage and analysis of molecules and cells involved in this process have shown the overwhelming importance of a dysregulated acute inflammatory response that causes enormous collateral damage from neutrophil products designed for the intracellular digestion of foreign pathogens. An understanding of the central importance of the frustrated host inflammatory response in causing structural and functional lung damage has led to the hypothesis that the direct suppression of inflammation can, independent of antimicrobial chemotherapy, ameliorate cystic fibrosis lung disease. The Cystic Fibrosis Foundation sponsored a four-year, multicenter, double-blind, placebo-controlled study of the use of alternate-day prednisone in patients with mild lung disease. Although the high-dose arm of 2 mg per kg produced unacceptable side effects, administering the lower-dose arm of 1 mg per kg resulted in sustained improvement in pulmonary function over the entire four-year period in patients colonized with *P aeruginosa*. Growth suppression after two years was the only major toxic effect. Thus, the treatment of earlier stages of lung disease with 1 mg per kg of prednisone on alternate days for as long as two-year cycles appears to be a promising new therapy. Further studies of the use of inhaled corticosteroids seem warranted to see if toxicity can be further limited while retaining efficacy.

If steroid therapy is effective, can nonsteroidal anti-inflammatory agents also favorably affect earlier stages of cystic fibrosis lung disease without the unwanted steroid side effects? A recently concluded four-year, double-blind, placebo-controlled trial of the use of high-dose ibuprofen showed a similar efficacy—virtually halting progressive lung function deterioration without any important toxic effects. In this study, however, it was clear that each patient needs an individually tailored pharmacokinetic evaluation to achieve a target peak plasma concentration of drug to suppress neutrophil ingress and activation in vivo. Plans are being made to provide a clinically useful pharmacokinetic analytic package to determine proper dosages.

In tandem with approaches to broadly suppress inflammation, efforts have been made to target specific mediators of inflammation, such as neutrophil elastase and other proteases. For this purpose, infused or inhaled antiproteases such as α_1-protease inhibitor (α_1-antitrypsin), recombinant human secretory leukoprotease inhibitor, and various synthetic peptide antiproteases have entered clinical trials. It appears that achieving concentrations of these suppressors sufficient to fully buffer the enormous load of free proteases in cystic fibrosis airways is the principal limiting factor to this approach. Drugs that suppress neutrophil activation, such as orally administered pentoxifylline, show promise.

In concert with inflammatory damage, ingress and activation of neutrophils result in a large burden of dying cells that release structural components into the airways. DNA and actin are two such structural components that are present in high concentrations and result in pronounced increases in viscoelasticity and adhesion tension of airways secretions. The genes for human deoxyribonuclease and gelsolin (the latter being a natural human protein that depolymerizes actin in a manner analogous to deoxyribonuclease's cleavage of DNA strands) have now been cloned, and recent clinical trials of recombinant human deoxyribonuclease (Pulmozyme, Genentech) have shown that, in patients with cystic fibrosis with mild to moderate lung disease, treatment can improve lung function by 5% to 10% for at least two years and reduce the frequency of pulmonary exacerbations requiring intravenous antibiotic therapy by 25% to 33%. Deoxyribonuclease was approved for use in patients with cystic fibrosis in early 1994, and it is safe and effective in patients with severe lung disease (forced vital capacity < 40% of predicted) and can also be used in patients during pulmonary exacerbations. Major questions regarding the future use of Pulmozyme include its role in early disease (children < 6 years or persons with normal or near-normal pulmonary function) and its long-term effect on the course of cystic fibrosis lung disease. Clinical trials of recombinant human gelsolin, which shows potent mucolytic activity and appears to be synergistic with Pulmozyme in vitro, are anticipated in 1995.

There has been recent progress in antimicrobial therapy also. A well-designed, multicenter, double-blind, placebo-controlled trial of inhaled tobramycin recently showed its safety and efficacy. In this trial, however, high doses of drug were used (to ensure sputum concentrations adequate to kill virtually all strains of *P aeruginosa*), delivered by an ultrasonic nebulizer unlike that currently used by most patients with cystic fibrosis. Recent trials of a new formulation of tobramycin delivered by commonly used jet nebulizers show promising results in achieving target levels in sputum. Further clinical trials leading to the Food and Drug Administration's approval of this new formulation specifically designed for cystic fibrosis therapy are underway. Another strategy, to boost host response to *P aeruginosa* by passively infusing opsonic antibodies to the mucoid capsular polysaccharide, is currently in clinical trials.

Much has been learned about the cellular consequences of the mutations in the *CF* gene that causes the disease. The *CF* gene product, cystic fibrosis transmembrane conductance regulator (CFTR), functions at least in part as a chloride channel. In addition, in a manner not yet elucidated, CFTR acts to regulate sodium transport in respiratory epithelia. These observations have led to investigation of a drug therapy capable of modifying chloride and sodium transport. The sodium channel blocker amiloride, when inhaled, has been shown to have a small but considerable beneficial effect on mucociliary clearance and pulmonary function in patients with cystic fibrosis and is currently being evaluated in clinical trials. In addition, nontoxic triphosphate nucleotides such as uridine triphosphate have been shown to enhance chloride secretion by stimulating alternate non-CFTR channels present in respiratory epithelial cells. Early clinical trials exploring the safety and efficacy of inhaled uridine triphosphate are in progress.

With the discovery of the *CF* gene, the prospect of replacement gene transfer therapy appeared on the horizon. Early clinical trials of in vivo gene therapy are underway at several centers. Much work remains to be done in identifying the proper target cells, refining gene delivery vectors to enhance efficiency of gene transfer to those cells, reducing host inflammatory and immune responses to vector components, and working out therapeutic indices, dose-response ranges, and dosing frequency. It is encouraging and exciting to note that more patients with cystic fibrosis have entered gene therapy trials than patients with all other human diseases combined, indicating the leading role that gene therapy is playing as medicine enters the molecular era of the 21st century.

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Use of Epoetin (Erythropoietin) in the Anemia of Prematurity

HEALTHY FULL-TERM INFANTS have a progressive fall in hemoglobin levels during the first several months of life, reaching a nadir of about 100 grams per liter (10 grams per dl) around 10 to 12 weeks of age. This physiologic anemia of infancy is due in part to the infant's rapid growth and expanding blood volume and in part to the decreased survival of erythrocytes. Hemoglobin levels fall earlier and more substantially in premature infants, particularly those born before 32 weeks of gestational age. In this group, the nadir may be as low as 60 grams per liter (6 grams per dl) and reached as early as 4 to 6 weeks of age. Infants with the anemia of prematurity often exhibit clinical signs of hypoxia, such as tachycardia, respiratory distress, and poor growth; this contrasts sharply with full-term infants who are usually asymptomatic.

The anemia of prematurity is a normocytic, normochromic anemia, characterized by low reticulocyte counts and bone marrow erythroid hypoplasia. Decreased erythropoiesis may be partially explained by increased concentrations of hemoglobin A (due to multiple blood transfusions), which decreases the hematopoietic stimulus. Erythropoietin levels in these patients are still 10-fold to 10,000-fold lower than expected for their degree of anemia, however. The most likely explanation for this inadequate erythropoietin response is a delay in the switch from liver to kidney as the primary organ of erythropoietin production. This switch, normally initiated late in the third trimester and completed just after birth, has not yet occurred in premature infants. These infants are unable to respond to hypoxia adequately, because the liver is less sensitive than the kidneys to low oxygen pressures.

Blood transfusions have traditionally been the treatment of choice for the anemia of prematurity, but alternative therapies have been sought because of the risks associated with transfusions. Recombinant human erythropoietin, first cloned in 1977, was shown in early studies to increase erythropoiesis in a dose-dependent manner by increasing the number of maturing erythroblasts, shortening the maturation period of developing erythrocytes, and increasing the release of reticulocytes from the bone marrow.

Early studies of the use of recombinant human erythropoietin (epoetin) in the anemia of prematurity showed an increase in erythropoiesis and a decrease in the need for transfusions when high doses of epoetin were used, along with adequate iron supplementation. Decreased weight gain was observed in the experimental groups of some early studies, but this was not observed when infants receiving epoetin also received high-caloric diets with protein supplementation. Substantial adverse effects were essentially nonexistent.

The promising results of these small early studies prompted a large, multicenter trial, the results of which were recently published. In this study of 241 premature infants, it was found that the administration of 750 U per kg per week of epoetin beta, along with 2 mg of elemental iron per kg per day, significantly reduced the need for transfusions and increased the average hematocrit. Weight gain was decreased in the experimental group, but a high-caloric diet was not used in this study. No adverse effects of epoetin beta were observed, except for a slightly higher incidence of infection. Two possibilities seem most likely to contribute to the higher incidence of infection: the administration of epoetin beta required multiple subcutaneous injections, two of the infants showing induration at the administration site; and treatment with epoetin beta causes an increased use of meager iron stores, which may increase susceptibility to infection. Although this trend in the study was not statistically significant, the observation signifies the need for caution in adopting this therapeutic approach. In other small studies in which infants received 3 to 6 mg of supplemental elemental iron per kg per day, no increased incidence of infection occurred.

Although the increased safety of blood transfusions through the use of single donors and improved viral screening techniques has reduced the risk of transfusion therapy, epoetin is emerging as a possible alternative in the treatment of the anemia of prematurity. Cost analysis has shown little difference between the two approaches. Transfusion therapy costs an average of $1,203 per infant and epoetin beta an average of $1,262. More studies are needed to establish optimal dosing regimens, iron supplementation, and nutritional support for patients receiving epoetin for the anemia of prematurity and to identify which patients are most likely to benefit. Further studies, however, may validate the use of epoetin to prevent or treat the anemia of prematurity.

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Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension

PERSISTENT PULMONARY HYPERTENSION is the most important cause of cardiorespiratory failure and the most common indication for treatment with extracorporeal membrane oxygenation (ECMO) in near-term neonates. In persistent pulmonary hypertension, the resistance to the flow of blood through the lungs is high. This results in hypoxemia caused by large right-to-left shunts through the patent ductus and the foramen ovale. Persistent pulmonary hypertension occurs as a primary condition of neonatal maladaptation or as a secondary condition to other diseases such as hyaline membrane disease, meconium aspiration, infection, and congenital diaphragmatic hernia. That most babies with this disorder also have severe parenchymal lung disease complicates their treatment and requires that therapy be aimed at both components. Babies with persistent pulmonary hypertension may also have varying degrees of perinatal hypoxic ischemic encephalopathy.

Nitric oxide is a recently discovered biologic messenger with many physiologic roles. It dilates blood vessels, allows macrophages to kill bacteria, fungi, and tumor cells, and is a neurotransmitter involved in central nervous system functions such as long-term memory. Nitric oxide is thought to be the final regulator of vascular muscle tone at a cellular level. It plays key roles in the regulation of cerebral and coronary blood flow and in overall vascular homeostasis. In humans, the presence of an endogenous inhibitor of nitric oxide synthesis has been suggested as a mechanism for the hypertension of chronic renal failure. Administered inhibitors of nitric oxide synthesis may have a beneficial effect on the hypotension of septic shock. Nitroso-containing compounds, such as nitroprusside, are thought to act through liberating nitric oxide in tissue.

The therapeutic value of inhaled nitric oxide is being studied in other conditions in which pulmonary hypertension plays a role and beyond the neonatal age group. These conditions include surgical and postoperative management of congenital heart disease, the adult respiratory distress syndrome, and idiopathic pulmonary hypertension.

To date, there is no clinically evaluated, selective pulmonary vasodilator that is free of systemic side effects. Studies using inhaled nitric oxide in animals have shown a reversal of pulmonary vasoconstriction, with no apparent effect on the systemic vascular resistance. In neonates and animals with persistent pulmonary hypertension, inhaled nitric oxide used in concentrations of 20 to 80 parts per million has been reported to rapidly improve preductal oxygen saturation. No studies, however, have shown whether inhaled nitric oxide decreases mortality or the need for ECMO in babies with persistent pulmonary hypertension or if it changes the incidence of chronic lung disease or the duration of a hospital stay.

The bedside set-up for administering inhaled nitric oxide should include primary-grade nitric oxide in nitrogen gas, 800 to 2,000 ppm, certified to contain no greater than 8 ppm of nitrogen dioxide and an electrochemical or chemiluminescence analyzer capable of measuring nitric oxide and nitrogen dioxide levels in parts per million. Currently available analyzers may give erroneous values of nitrogen dioxide in the presence of a high fraction of inspired oxygen or may not readily fit in a ventilator circuit. Other hardware includes single-stage diffusion-free regulators, an appropriate flowmeter, and a scavenging system.

Once it reaches the pulmonary circulation through the lung, inhaled nitric oxide almost instantly binds to

reduced hemoglobin, forming nitrosyl-hemoglobin, which is then oxidized to methemoglobin with the production of nitrites and nitrates. Provided methemoglobin levels in the blood remain below 5%, this leads to no clinically important problems. Inhaled nitric oxide does get into platelets and prolongs bleeding time, which has raised the concern that this might lead to an increased risk for neonatal intracranial bleeding. Nitric oxide and its oxidation products (NO_2, NO_x) may also cause direct pulmonary toxicity, particularly to immature lungs. Current occupational safety and health standards consider exposure to 25 ppm for an 8-hour time-weighted average safe. Pulmonary vasodilator concentrations of nitric oxide currently used are in this range, but therapy with nitric oxide will usually involve a 24-hour exposure rather than 8 hours.

Most investigators feel that inhaled nitric oxide is still an experimental therapy, but some centers are currently using inhaled nitric oxide for clinical indications, outside of experimental protocols. Theoretically, any center, large or small, could avail itself of the equipment and know-how to administer inhaled nitric oxide at this stage. Undesirable effects of this might include delayed referral of patients needing level III care and exposure of patients to a possibly toxic gas before its indications, contraindications, and side effects have been fully elucidated by randomized controlled trials in progress.

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Dialysis and Renal Transplantation of Infants

OBSTRUCTIVE UROPATHY, renal dysplasia, and renal cortical necrosis are the most common causes of end-stage renal disease in infants. An interesting occurrence is that asphyxia in the newborn period can damage kidneys out of proportion to brain, leaving an infant with renal cortical necrosis but good potential for intellectual development. Oxalosis and severe congenital nephrotic syndrome are infrequent causes of renal failure.

When infants with severe renal disease fail to grow with conservative management, dialysis may be needed to help an infant grow to a size suitable for transplantation. Dialysis is usually prescribed as a vigorous peritoneal dialysis program, with the infant receiving 12 or more exchanges a day. Besides this dialysis prescription, adequate nutrition must be provided. Infants with renal failure generally have poor appetites, and 90% of them need nasogastric tube feeding or gastrostomy feeding. Daily energy intakes of as much as 140 kcal per kg of body weight may be needed. With such a dialysis and nutrition program, however, growth and development can be well supported and transplantation undertaken if the renal disease does not resolve.

Kidney transplantation is the therapy of choice for infants and children with end-stage renal disease. Transplantation has been accomplished in infants as small as 4.5 kg (10 lb), but is more easily done, with less risk, once the infant has reached 8 to 10 kg (18 to 22 lb). At this size, when the transplantation is done at a center with both a surgeon and nephrologist experienced in caring for infants, the results approach those attained in larger children. Patient survival rates are above 95% at one year and graft survival above 90%. Most donors (70%) used for infants and small children are living-related, usually a parent. Best results are obtained with the use of living donors. Cadaver donors younger than 6 years are not suitable because of rates of graft thrombosis and technical complications.

The kidney is placed in the peritoneal cavity, with anastomoses of the renal artery and vein end-to-side to the aorta and inferior vena cava. The kidney most often lies on the right side, and the right native kidney may be removed to make room. Both native kidneys are removed only if they are thought to be a risk for infection or the cause of severe hypertension. In the immediate postoperative period, urine output is high, but the adult kidney accommodates to the infant's physiology within days.

Infants and small children usually grow and develop well after transplantation. Most are maintained on triple immunosuppressive therapy consisting of azathioprine, cyclosporine, and low-dose prednisone. Tacrolimus (Prograf, called FK 506 during clinical trials before US Food and Drug Administration [FDA] approval) is similar to cyclosporine in action and has recently been approved by the FDA for use in patients with liver transplants. It may also have a role in kidney transplantation, particularly in patients who do not tolerate cyclosporine or who absorb it erratically. Tacrolimus is absorbed rapidly from an empty stomach. New and better immunosuppressive regimens, with better efficacy and fewer side effects than this triple therapy, are on the horizon. If a transplanted kidney does fail, retransplantation is possible.

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Sedation for Pediatric Procedures

THE INCREASE IN the number of diagnostic and therapeutic procedures done on infants and children over the past decade has led to an increased use of sedation for these patients. Imaging studies, bone marrow aspirations, lumbar punctures, dental procedures, cardiac catheterizations, and endoscopies are commonly done with sedation in hospitals and ambulatory clinics. The American Academy of

Pediatrics Committee on Drugs and the Joint Commission on Accreditation of Healthcare Organizations have focused attention on the care and comfort of infants and children during these procedures. The promotion of practice guidelines by these organizations is aimed at reducing risk and ensuring quality by reducing variations in practice.

The decisions to perform a procedure and to sedate a patient are independent of one another. Too often physicians ignore nonpharmacologic methods, such as sleep deprivation and natural sleep, cuddling, and distraction, that can be successful and eliminate or reduce the need for sedating drugs. A rational approach requires the answers to a series of questions about the procedure: Is it painful? How long must the patient be sedated? Is immobility necessary? Is this procedure an emergency? The answers, combined with a careful assessment of the patient, allow individual decisions to be made. The assessment includes a medical history and physical examination, looking for a history of apnea, seizures, previous sedations, cardiopulmonary problems, current medication use, or recent illness. The examination may reveal a possible airway problem. There is no doubt that the time and effort involved in this aspect of the sedation process will yield a great return in terms of patient safety and success of the procedure. Thoughtful physicians will then be in a position to assign the level of risk, to choose the appropriate drug, and to ensure patient safety with the most appropriate monitoring and personnel.

The level of sedation achieved when administering sedative drugs ranges from conscious sedation to a level near that of general anesthesia. Recognizing this continuum of sedation and individual patient variability in response to sedating drugs, it is mandatory that patients be monitored and assessed throughout the procedure and recovery. The safety net includes the regular assessment of physiologic variables by personnel trained in basic life support and immediately available emergency equipment and a responsible physician. Protocols are necessary to ensure consistency, but in any situation, vigilant attention to the patient is key.

A recent survey of current practice in which the first three choices for sedation were chloral hydrate, DPT (meperidine hydrochloride [Demerol], promethazine hydrochloride [Phenergan], and chlorpromazine hydrochloride [Thorazine]), and pentobarbital indicates that clinicians use drugs that are familiar to them. Many alternative pharmacologic agents are available that have more desirable properties and fewer side effects than these agents.

Medications available to clinicians fall into several categories. Sedative-hypnotic drugs include barbiturates, benzodiazepines, and major tranquilizers (butyrophenones). Characteristics such as rapidity of onset, duration of effect, and side effects vary widely. For example, barbiturates enhance the perception of pain despite their sedative properties, whereas butyrophenones enhance the effects of analgesics. The choice between these two classes of drugs, therefore, should be influenced by whether or not the procedure planned will be painful to the child.

Opiates—often referred to as narcotics—are primary analgesics with sedative side effects, and all are potent respiratory depressants. Several new synthetic opiates are short-acting and are ideal for brief painful procedures because they do not leave the child depressed for a lengthy period. Local anesthetics are important to use in every case in which the medical procedure involves any degree of pain because the local anesthetic will reduce the required dose of opiates or sedatives, thus increasing the safety to the patient.

Adjuvant medications such as the nonsteroidal anti-inflammatory drugs, particularly the newer parenteral drug ketorolac tromethamine (which is not yet approved for pediatric use), have analgesic effects nearly equal to those of the opiates and are devoid of respiratory depression, thereby reducing the opiate requirement and enhancing safety. General anesthetics, such as nitrous oxide, ketamine hydrochloride, and propofol in subanesthetic doses, can occasionally be used by nonanesthesiologists. We recommend training and experience as a prerequisite to the use of such drugs and adherence to strict protocols to prevent trespass into the realm of general anesthesia by nonanesthesiologists. Each drug, furthermore, has important dose limitations, side effects, and possible complications of which physicians must be aware.

Each institution must develop therapeutic guidelines based on local practice and institutional experience. Departments of anesthesia are increasingly being consulted in the development of protocols and guidelines. This trend is entirely appropriate because new pharmacologic agents are often introduced as anesthetic agents. The administration of sedation will remain most often in the practice of nonanesthesiologists, however. Each practitioner must define the scope of practice based on personal knowledge and skills and seek appropriate consultation for those patients who are beyond that scope.

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Alerts, Notices, and Case Reports

Allopurinol Hypersensitivity Syndrome Revisited

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ALLERGIC DRUG REACTIONS continue to be the leading cause of iatrogenic illness in adults.[1] Since the first case of allopurinol hypersensitivity was reported in 1970, more than 100 cases have subsequently been reported in the literature.[2] It is noteworthy how infrequent this reaction is in light of the 240 million doses that are prescribed annually.[3] Yet, although rare, this life-threatening reaction is often preventable if caution is exercised and dosages in patients with renal insufficiency are modified. We report a case of severe allopurinol hypersensitivity syndrome that manifested many features typical of sepsis along with advanced renal and hepatic dysfunction.

Report of a Case

The patient, a 42-year-old woman with hypertension, insulin-dependent diabetes mellitus, mild renal insufficiency, and gout, was admitted to the hospital for the evaluation of fevers, night sweats, rapidly progressive renal insufficiency, and a diffuse maculopapular rash. Ten days before admission, a rash developed predominantly on the patient's abdomen and lower extremities, and she was seen in the outpatient clinic. She was noted to be taking insulin, furosemide, captopril, nifedipine, colchicine, and allopurinol.

There was no history of antibiotic use. The patient's allopurinol therapy was discontinued at the time of her initial evaluation, and the rash faded. The rash recurred, however, along with fevers and night sweats two days before admission. On her admission to the medical intensive care unit, the patient appeared ill, had a temperature of 38.4°C (101°F), a pulse rate of 114 beats per minute, and a blood pressure of 110/40 mm of mercury. The findings of the examination were notable for erythroderma of the face, neck, and arms, along with an erythematous maculopapular rash of the abdomen and lower extremities. Her other physical findings were normal.

Initial laboratory tests revealed a leukocyte count of 15×10^9 per liter with 0.67 segmented neutrophils, 0.15 bands, 0.08 lymphocytes, and 0.06 eosinophils. Her blood urea nitrogen level was elevated at 40.0 mmol per liter (112 mg per dl); serum creatinine, 795.6 μmol per liter (9.0 mg per dl); aspartate aminotransferase (formerly SGOT), 115 IU per liter; and alanine aminotransferase (formerly SGPT), 446 IU per liter. A urinalysis was notable for moderate proteinuria, granular casts, and pyuria. A Hansel's stain for urinary eosinophils was negative. The most recent creatinine level before the onset of this illness was 380 μmol per liter (4.3 mg per dl).

Because of a concern regarding sepsis in the setting of her renal dysfunction and hypotension, pulmonary artery catheterization was done, revealing a cardiac output of 9.0 liters per minute, systemic vascular resistance of 400 dynes per second per cm, and a pulmonary capillary wedge pressure of 18 mm of mercury. Further evaluation included an echocardiogram that did not reveal vegetations and abdominal and pelvic computed tomographic scans that were normal.

The patient was treated with empiric broad-spectrum antibiotic therapy after specimens of blood, urine, and sputum were sent for culture. Consultations were obtained from the dermatology service as well as the critical care and infectious diseases services. Multiple skin biopsies were taken, and all of her ongoing medications, except for insulin, were discontinued.

On hospital day 3 the patient's skin was desquamating, she was persistently febrile, and her leukocyte count was 27×10^9 per liter with 0.15 eosinophils. Her aminotransferase values remained elevated, and she became progressively anuric. All cultures remained negative, however, as were viral serologic tests for hepatitis.

At this time, the results of her skin biopsies returned, and the specimens revealed a mild spongiotic epidermis with a dermis that contained lichenoid and superficial perivascular lymphohistiocytic infiltrates with eosinophils, consistent with a drug eruption. The diagnosis of an adverse reaction to allopurinol was entertained given her aforementioned history. Hemodialysis and a regimen of methylprednisolone sodium succinate, 125 mg intravenously every six hours, were begun, and the antibiotics were discontinued. The steroid doses were rapidly tapered over a five-day period. One day after beginning this treatment, the patient's fever defervesced, her eosinophilia resolved, and her sense of well-being markedly improved. An oxipurinol concentration measured 14 days after her last dose of allopurinol and after one hemodialysis session was elevated at 9.3 μmol per liter. Peak oxipurinol concentrations after a single 300-mg dose of allopurinol are about 5.0 μmol per liter (ARUP, Salt Lake City, Utah).

Ten days after admission the patient was discharged; she remained afebrile, her desquamation was resolving, and laboratory abnormalities were returning to normal, although she continued to require dialysis. Serologic

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tests for antinuclear antibody, human immunodeficiency virus, and hepatitis were all negative. Twelve days after discharge, the patient was noted to have recurrence of her erythematous maculopapular rash and had a leukocyte count of 16×10^9 per liter with 0.32 eosinophils, but she was otherwise asymptomatic without aminotransferase elevation while being dialyzed three times a week. At this point, glucocorticoid therapy was reinstituted and tapered over a two-week period. The eosinophilia resolved, and the maculopapular rash gradually faded without progression. The patient required continued hemodialysis for an additional two months but subsequently became stable with a serum creatinine level of 486 μmol per liter (5.5 mg per dl). Except for the allopurinol, all other medication regimens have since been reinstituted without further complications.

Discussion

The allopurinol hypersensitivity syndrome is defined by a clear history of allopurinol use; a clinical picture consisting of two of the following major criteria or one major and one minor criteria: major: rash (diffuse maculopapular or exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis), worsening renal function, or acute hepatic toxicity; minor: fever, eosinophilia, or leukocytosis; and a lack of exposure to another drug that may have caused a similar clinical picture.[4] The rash may change over time, with the most common pattern being a maculopapular pattern evolving into exfoliative dermatitis. If steroids are used, the rash might recur with tapering, as evidenced in this case.[5] The leukocytosis is often characterized not only by eosinophilia, but also by the presence of band forms without clear evidence of infection. Indeed, our patient had a substantial number of bands on her peripheral smear, and her clinical picture initially was highly suggestive of sepsis. Many patients have underlying chronic diseases, with renal insufficiency, hypertension, diabetes mellitus, and congestive heart failure being the most common. Consequently, these patients are typically on concomitant medication regimens, including diuretics. Some have speculated that the coadministration of thiazides, in particular, may predispose to the development of this syndrome.[6] This is presumably related to the thiazide diuretics inhibiting the excretion of oxipurinol, resulting in excessively high blood concentrations. Onset is typically two to six weeks after beginning treatment, but the range is large—1 to 728 days. Most patients are on a dosage of 300 mg per day, despite having underlying renal insufficiency. Overall mortality in the reported cases is about 25%.

The likely mechanism of toxicity is a hypersensitivity reaction to allopurinol or its major metabolite, oxipurinol, leading to immune complex deposition and diffuse vasculitis. Almost all organs have been involved. The accumulation of oxipurinol correlates with the development of the syndrome. Because oxipurinol clearance is directly related to renal function, allopurinol hypersensitivity is closely associated with renal insufficiency.[7] Although the half-life of oxipurinol is about 20 hours in patients with normal renal function, it is 250 hours when a patient has anuria.[8] This long half-life explains why our patient still had an oxipurinol level of 61 μmol per liter 14 days after her last dose. We note that earlier serum specimens were unavailable for assay. Other risk factors in addition to the reduced renal function for the development of the sensitivity syndrome include advanced tophaceous gout, chronic alcoholism, and severe liver disease.[9]

No effective treatment exists. Steroid therapy has been advocated by some,[10] although the sum of the data does not suggest a beneficial effect.[11] Oxipurinol can be removed from the body fluids by dialysis, and this has occasionally been beneficial.[12] As our patient was concomitantly started on hemodialysis, it is difficult to comment on the benefits of steroids, although some benefit seems to have been derived when the rash recurred and a more gradual taper was attempted.

Clearly early recognition of the syndrome, withdrawal of the drug, and supportive care remain the mainstay of therapy. In a patient for whom allopurinol therapy is clearly indicated, the dosage must be adjusted for renal function because this appears to be a major risk factor for the development of this syndrome. The importance of an approved indication cannot be overemphasized, given the fact that in more than half of the cases in the literature, treatment was being given for asymptomatic hyperuricemia.

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Multiple Organ Dysfunction in a 33-Year-Old Woman Due to Hereditary Hemochromatosis

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MULTIPLE ORGAN DYSFUNCTION due to iron overload in patients with hereditary hemochromatosis is a preventable process, if the disorder is recognized early enough. Furthermore, some degree of organ dysfunction is often reversible with prompt implementation of appropriate treatment. Early diagnosis of this disease is crucial. Hemochromatosis symptomatically affects men in the fifth and sixth decades of life more often than women or younger men. The most frequent symptoms are weakness, lethargy, loss of libido, weight loss, and arthralgia. Later in the course of disease, it can lead to the development of diabetes mellitus or other organ failures such as that of liver or heart.[1] Although the signs and symptoms of hereditary hemochromatosis are usually less evident in menstruating women and younger men, it is important to be aware that this disease can affect both women and younger men as well.* Herein we present a case of hereditary hemochromatosis in a woman of childbearing age with substantial clinical manifestations, including new-onset diabetes, liver dysfunction, cardiac hypokinesis, and secondary hypogonadism.

Report of a Case

In October 1993, the patient, a 33-year-old woman with a 12-year history of amenorrhea, presented to the Emergency Department of Harbor-UCLA Medical Center with new-onset diabetes mellitus. She had progressively worsening nausea, vomiting, polyuria, polydipsia, malaise, and a 6.8-kg (15-lb) weight loss over three weeks. Her medical history included a left wrist fracture seven months before admission that was repaired by a bone graft from her right hip. The graft harvest site became infected, for which she received an eight-week course of antibiotics. She also had had meningitis as a teenager. She had two therapeutic abortions at ages 20 and 21. Shortly after the second abortion, the patient became amenorrheic. She had never had blood transfusions. She had smoked one pack of cigarettes per day for 15 years and drank alcohol occasionally but heavily at times. The family history was unremarkable for diabetes mellitus, cardiovascular disease, or hematologic disease.

On physical examination, the patient appeared anxious, was thin, and had a temperature of 37°C, a pulse rate of 77 beats per minute, blood pressure 99/66 mm of mercury, and respiratory rate 14 per minute. The skin over the entire body was noted to be light bronze. There was shotty, bilateral, anterior cervical lymphadenopathy. The lungs were clear to auscultation. The cardiac rhythm was regular, and the rate was normal. The abdomen was nontender, with a liver span of 10 cm.

Laboratory values were as follows: leukocyte count, 9.3×10^9 per liter (9,300 per mm^3); hemoglobin, 155 grams per liter (15.5 grams per dl); hematocrit, 0.44 volume fraction; platelet count, 102×10^9 per liter (102,000 per mm^3); serum sodium, 135, potassium, 4.9, chloride, 88, and bicarbonate, 19 mmol per liter; blood urea nitrogen, 3.4 mmol per liter (9 mg per dl); creatinine, 44.2 μmol per liter (0.5 mg per dl); glucose, 22.0 mmol per liter (397 mg per dl); serum acetone 3+; alanine aminotransferase, 93 U per liter; aspartate aminotransferase, 59 U per liter; alkaline phosphatase, 122 U per liter; albumin, 45 grams per liter (4.5 grams per dl); prothrombin time, 11.7 seconds; and partial thromboplastin time, 35.8 seconds.

An electrocardiogram showed sinus rhythm with multiple premature atrial complexes and nonspecific lateral T-wave changes. In addition, it showed low voltage in the frontal plane. A subsequent echocardiogram revealed a decreased left ventricular ejection fraction of 25%, with moderate mitral regurgitation. Radionuclide imaging confirmed the low ejection fraction.

A serum prolactin level was 9 μg per liter (9 ng per ml; normal, 0 to 25 ng per ml), a luteinizing hormone level was less than 3 IU per liter, the follicle-stimulating hormone level was less than 1.2 IU per liter, and total serum estrogen level was 41 ng per liter (normal, 61 to 394 ng per liter).

Finally, the iron studies showed an iron saturation of 92% with a serum iron level of 26.3 μmol per liter (147 μg per dl) and a total iron-binding capacity of 28 μmol per liter (159 μg per dl). The serum ferritin value was 4,290 μg per liter (4,290 ng per ml).

Based on the laboratory results, a liver biopsy was done that established the diagnosis of hemochromatosis. The biopsy specimen showed that the liver had a predominantly nodular pattern. Micronodules of liver were surrounded by fibrous tissue with focal bile duct metaplasia. The hepatocytes, Kupffer cells, and bile duct epithelial cells contained a granular golden pigment. These cells stained strongly positive with Prussian blue stain for iron (Figures 1, 2, and 3). HLA typing revealed the presence of the *A3* gene.

*See also the editorial by L. H. Smith Jr, MD, "Pumping Iron," on pages 370-372 of this issue.

(Niihara Y, Brouwer DW, Cantos KA: Multiple organ dysfunction in a 33-year-old woman due to hereditary hemochromatosis. West J Med 1995; 162:362-364)

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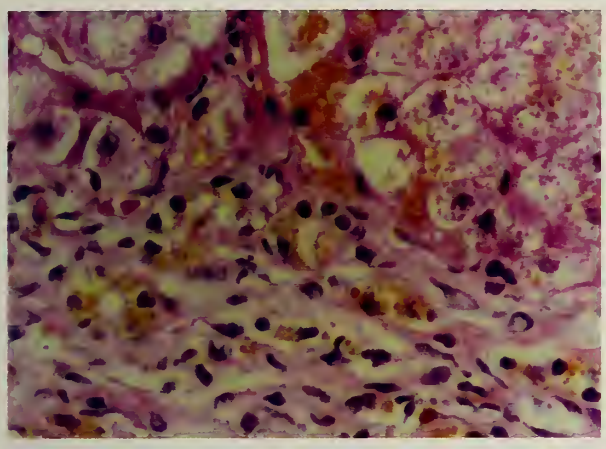

Figure 1.— A liver biopsy specimen shows hepatocytes filled with hemosiderin (light brown intracellular material [hematoxylin and eosin stain; original magnification, ×400]).

Discussion

Hereditary hemochromatosis is characterized by excessive absorption and accumulation of iron in various tissues. The early clinical manifestations include general symptoms such as weakness, lethargy, loss of libido, and weight loss. It also frequently causes arthralgia. The organs most frequently involved include the pancreas, liver, heart, endocrine organs, and skin.[1-3] A typical description of a patient with advanced disease is of a white man in the fifth to sixth decade of life with bronze-colored skin, diabetes, and testicular atrophy. The basic pathogenesis of iron accumulation is a genetic defect that results in increased iron absorption by the intestines.[3] These patients often carry the *HLA-A3* gene, which the patient in this report was found to carry.[4,5] Affected persons absorb about two to three times more iron per day than a normal person[2,3]—that is, about a 1- to 3-mg net gain of iron per day. When a cumulative iron load of 15 to 35 grams is reached, the person may become symptomatic.[2] Therefore, it usually takes 40 to 50 years before the disease may manifest itself clinically. In the case of a female patient, it is thought that iron loss due to menstruation and a relatively lower intake of iron delays or eliminates clinical manifestations of the disease.[2,6,7]

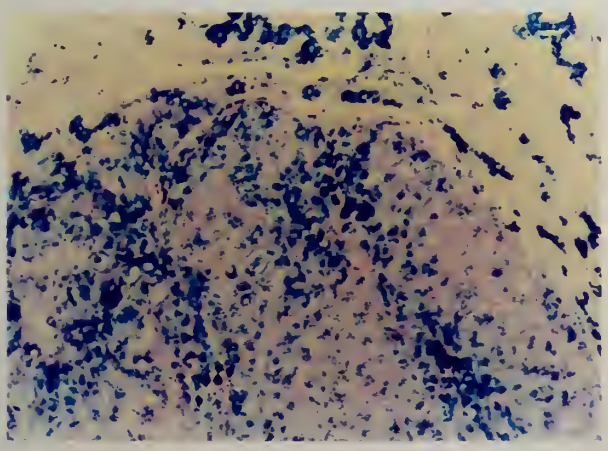

Figure 2.—Iron stain of the liver biopsy specimen shows substantial accumulation of iron in hepatocytes (Prussian blue stain; original magnification, ×100).

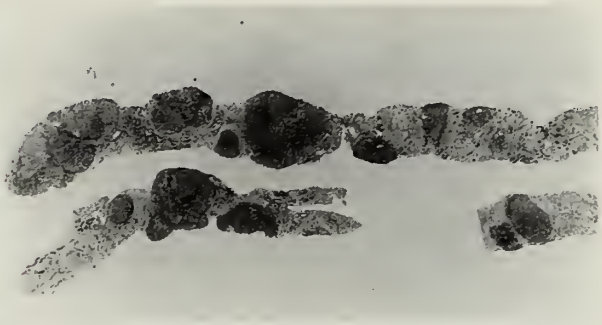

Figure 3.—Extensive micronodular cirrhosis consistent with severe hemochromatosis was noted in the liver biopsy specimen (hematoxylin and eosin stain; original magnification, ×20).

It is recognized that clinically symptomatic disease is seen in 1 in 200 people, but a heterozygous carrier for hemochromatosis may be found in 1 in 10 whites.[2,4] With a screening test of transferrin saturation, a value of 50% identifies nearly all persons who are homozygous for the disorder, regardless of sex or iron burden.[4] To make screening more specific, suggested threshold values for transferrin saturation during fasting are 60% for men and 50% for women.[4]

The case presented here is not unique from the standpoint of gene frequency, because white women have as high a gene frequency as white men. It is unique, however, for the age that clinical manifestations occurred and for their severity. The incidence of symptomatic hereditary hemochromatosis is much lower among women than men because of the factors mentioned earlier. In addition, even if the disease becomes clinically apparent, the age of onset is much later than that seen in our patient, usually in the fifth or sixth decade.[2,4] Our patient became amenorrheic at age 20. The cause of amenorrhea is likely secondary hypogonadism due to iron deposition in the anterior pituitary gland. The amenorrhea may be attributed to Asherman's syndrome brought on by a therapeutic abortion done just before the onset of her amenorrhea,[8] and it may be argued that the lack of menstruation and her history of alcohol intake exacerbated the rate of iron accumulation over the subsequent ten years. Even then, to have such substantial iron accumulation by age 33 is most unusual. In a search of the literature, only two other reports of symptomatic hereditary hemochromatosis with diabetes mellitus, secondary hypogonadism, and skin color change in young adult women were found.[9-11]

An advanced stage of hereditary hemochromatosis in a young woman is rare, but may not be difficult to

diagnose as the signs and symptoms are distinctive. On the other hand, less symptomatic or asymptomatic cases of hereditary hemochromatosis are likely to be underappreciated. Some of the early symptoms of hemochromatosis—weakness, lethargy, loss of libido, arthralgia—may be indistinguishable from those of more common disorders, and clinicians may need to consider hemochromatosis more frequently in the presence of these.[2] The patient's age or sex should not be a reason to exclude hereditary hemochromatosis from the differential diagnosis.

Screening for hemochromatosis is accomplished relatively easily. Some authors have advocated that the iron status of every patient be screened to evaluate for both iron overload and iron deficiency.[6] Although physicians may not consider measuring iron levels and total iron-binding capacity on every patient, they should keep in mind that hemochromatosis may be more prevalent than they think. It is important to prevent or reverse the complications of hemochromatosis with appropriate management during the early clinical stages.[12] It is especially important to note that women of childbearing age are not always protected from the clinical consequences of hereditary hemochromatosis, as exemplified by this case report.

We have described a common disorder with a rare presentation. Apparently no group is completely protected from this disease, including young women. Because the consequences of hereditary hemochromatosis are preventable or reversible to some degree with prompt treatment, early recognition of the disease is vital. Our case shows that a patient's being young or female should not be a reason to exclude hereditary hemochromatosis from the differential diagnosis when findings are suggestive of this disorder.

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Multiple Stress Fractures

An Unusual Presentation of Cushing's Disease

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STRESS FRACTURES occurring as a result of overzealous sports activities have become commonplace, but multiple stress fractures other than in a symmetric distribution are unusual. In the case reported here, the finding of multiple areas of abnormal uptake on a bone scan might have been mistaken for metastatic disease. Additional questioning of the patient and the often-requested "clinical correlation" led to the correct diagnosis of Cushing's disease. This case emphasizes the importance of the clinical history and the correlation of plain radiographs in interpreting skeletal scintigraphic findings.

Report of a Case

The patient, a 30-year-old woman, was seen initially with bilateral hip pain of one month's duration. The pain radiated to the groin and was aggravated on rising from a seated position. She had carried a diagnosis of schizoaffective disorder for the previous nine years. Her current medications were haloperidol, 10 mg at bedtime; trazodone hydrochloride, 300 mg at bedtime; and lorazepam, 0.5 mg twice a day.

An anteroposterior film of the pelvis showed an unusual crescentic lucency over the left pubis, resembling a "vacuum phenomenon" (Figure 1), and bilateral degenerative changes at the hips. Also noted was diffuse osteopenia. The rest of the pelvis was judged unremarkable, although visualization of the sacroiliac joints was suboptimal because of the patient's body habitus. A bone scan was recommended because the unusual appearance of the pubic lesion suggested the possibility of pathologic fracture.

The bone scan (Figure 2) showed multiple foci of abnormal tracer uptake consistent with fractures involving C-7, several ribs, the sacrum and sacroiliac joints, both iliac fossae, and the left superior and inferior pubic rami. Also noted were areas of increased activity along the medial proximal tibial diaphysis and in the metatarsal bones (Figure 3). On further questioning in the nuclear medicine department, the patient reported that for the past month

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Figure 1.—The detail of an anteroposterior radiograph of the pelvis shows a left superior pubic ramus fracture with a vacuum phenomenon.

she had engaged in daily three-hour, high-intensity aerobic exercise and walking in an attempt to lose weight. On review of her medical record, the following were noted: a 6.8-kg (15-lb) weight gain over the past two years, easy bruising for the past five years, worsening acne, and a rounded, somewhat reddish face. Correlation with the available plain radiographs suggested multiple stress fractures and, in this case, insufficiency fractures due to osteoporosis.

The finding of multiple insufficiency fractures on the bone scan, additional history, and the patient's cushingoid appearance prompted further workup for presumed Cushing's syndrome. The AM serum cortisol level was mildly elevated, and the 24-hour urine cortisol level was markedly elevated at 2,200 nmol per day (normal, 30 to 300 nmol per day). A serum corticotropin (formerly

Figure 2.—Posterior and anterior views of the bone scan reveal multiple foci of increased uptake in the anterior C-7 vertebra, ribs, sacrum, sacroiliac joints, iliac fossae, and the superior and inferior left pubic rami.

Figure 3.—An anterior view of a lower extremity bone scan shows stress phenomena, including two areas in the proximal and midleft tibial diaphysis, and in the metatarsal bones bilaterally.

ACTH) level was measured at 13 pmol per liter (normal, 4 to 22 pmol per liter), and the results of subsequent dexamethasone suppression testing, low- and high-dose, as well as corticotropin-releasing hormone and metyrapone testing, were all consistent with a diagnosis of pituitary Cushing's disease. This was confirmed by magnetic resonance imaging of the sella, which showed a 5-mm pituitary adenoma. The patient underwent transsphenoidal resection. The histologic diagnosis was amphophilic corticotropin-producing pituitary adenoma.

Following the resection, her cortisol and corticotropin values fell to normal levels. Now, two years after her operation, she is doing well, has lost 9 kg (20 lb), and has no laboratory evidence of hormonal imbalance. Her psychiatric symptoms persist, and she has continued on her psychiatric medications.

Discussion

Cushing's syndrome is the clinical and metabolic disorder resulting from glucocorticoid excess. Cushing's disease refers to the condition where excess corticotropin is secreted due to hypothalamic-pituitary dysfunction.

There are many clinical manifestations, including central obesity, moon facies, and cutaneous changes including facial ruddiness, thinning of the skin, easy bruising, acne, and hirsutism. Notable as well in this case are osteoporosis and mood alterations. Depression is a common symptom and should also be considered in the differential diagnosis.[1] In this particular patient, it is striking to note how many of her symptoms were possibly attributed to her psychiatric diagnosis. Her weight gain led to an exercise regimen that in turn led to multiple stress and insufficiency fractures due to her underlying osteoporosis.

Stress fractures occur as a result of normal stress on abnormal bone or abnormal stress on normal bone. Stress fractures occurring in normal bone may be referred to as fatigue fractures, whereas those occurring in abnormal (such as osteoporotic) bone are usually called insufficiency fractures.[2] The term pathologic fracture is best applied to a fracture occurring in bone weakened by tumor.[3]

Conditions predisposing to insufficiency fractures include osteoporosis, osteomalacia and rickets, rheumatoid arthritis, osteogenesis imperfecta, osteopetrosis, Paget's disease, hyperparathyroidism, and others.[3] This case of Cushing's disease presenting with multiple fatigue and insufficiency fractures also points out the importance of whole-body skeletal scintigraphy in problematic cases. The multiplicity of fractures was not evident from the radiographs initially ordered (anteroposterior view of the pelvis).

The most common differential considerations when there are multiple sites of abnormal increased uptake on skeletal scintigraphy include metastatic disease, fractures from multiple trauma, arthritis, Paget's disease, and postsurgical changes. Less common considerations would include aseptic necrosis, polyostotic fibrous dysplasia, lymphoma, multiple myeloma, hematogenous osteomyelitis, metabolic bone disease, multifocal primary bone tumors, and stress fractures.[4] The pattern of abnormal uptake may suggest the clinical disorder such as medial knee joint involvement in osteoarthritis or the linear distribution of multiple contiguous rib fractures.

Most stress fractures occur in the lower limbs, particularly in the tibias, and less commonly in the femurs and the feet (metatarsals, sesamoids, navicular, calcaneus). Rare stress fracture sites, as seen in this case, include the pubic and sacroiliac joint regions and ribs.[5] Osteoporotic insufficiency fractures may occur in the sacrum and are often radiographically occult.[6] Multiple stress fractures are unusual, except in the case of insufficiency fractures resulting from systemic disease and in bilateral symmetrical stress fractures in the lower limbs.[7] Two additional cases of cortisol-induced osteoporosis in female athletes, discovered after the occurrence of multiple and unusual fractures, have been reported recently.[8] Both women had substantially diminished bone mineral density, which showed partial reversal following therapy. Although bone densitometry was recommended in our case, it was never requested by the clinicians. It is doubtful that the results would have changed the patient's treatment.

The bone scan remains the most sensitive imaging modality to diagnose stress-related injuries to bone.[9-11] As in other osseous pathologic processes—metastases, osteomyelitis, infarction—scintigraphy has the potential for demonstrating lesions and multiplicity earlier than roentgenography.[12,13] In addition, certain sites of stress fractures have characteristic scintigraphic findings ranging from an ill-defined cortical area of increased radiotracer uptake to an extensive transcortical area of intense increased activity.[5,13,14]

Our patient's report of exuberant exercise activity, combined with the pattern of abnormalities and the confirmatory plain film findings, led to the correct conclusion of multiple stress fractures—both fatigue and insufficiency fractures related to underlying osteoporosis. It remained for her clinicians to determine the predisposing disease state and to make the final diagnosis of Cushing's disease.

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History of Medicine

James Lind's Legacy to Clinical Medicine

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Based on a talk given in acceptance of the 1994 Golden Apple Award, presented by the California Medical Association to recognize exceptional physicians who have made a lifelong commitment to teaching.

An 18th-century exemplar of an astute clinician was James Lind of Edinburgh, Scotland. Long before the discovery of malarial parasites, Dr Lind questioned sailors about where they had traveled before their shaking chills began. He wisely advised them to go ashore in the tropics only in the daytime and to sleep offshore aboard ship. Most ships would have been anchored beyond the range of mosquitoes likely to forage for blood at night. James Lind also invented a simple portable still to desalinate seawater and made numerous other contributions to the health of seafarers. His greatest discovery was a sure cure and preventive for scurvy, an ancient curse.

Because the word "scurvy" was never used until the Middle Ages—and then often inaccurately—how do we know that it was a problem in antiquity? We find the disease's distinctive features described in the Ebers Papyrus about 1700 BC; in texts of Susruta, the great Indian surgeon, about 400 BC; in the writings of Hippocrates; in accounts of Pliny the Elder, a first-century Roman; and in the works of Chang Chi, known as "the Galen of China," about 200 AD. The sketchy vignettes of those ancient physicians signify scurvy to us only because of much later and much more detailed descriptions—none more vivid than James Lind's.

Drawing on his own careful histories and physical examinations, he described scurvy as follows:

> In the early stages, patients do not look very sick, but are listless, perhaps a little pale, and have an aversion to exercise. They still eat well, but in a few days develop universal lassitude, stiffness, and feebleness of the knees, some difficulty breathing, itchy gums, and rough, dry skin splattered with bluish and reddish spots. These hemorrhages vary from the size of a lentil to a handsbreadth, mostly on the legs, less on the arms and trunk, and rarely on the head or face. The gums, however, bleed readily and become first soft and spongy and then putrid and rotten. The breath is foul, and the teeth fall out. The legs swell, at first only in the evening, but later all the time. Ulcers appear on the thighs, coated with blood and gore, and will not heal. Broken bones will not mend and even old, healed wounds may break apart. The patients are now susceptible to whatever infection is going around, often diarrhea. Many joints, but especially the knees, are very painful and greatly swollen with blood. Patients now have abdominal pain, cannot eat, are jaundiced and swollen all over, breathe with pain and labor, and may die suddenly.

"It is not easy," Dr Lind wrote, "to conceive a more dismal and diversified scene of misery."

Scurvy occurred on land, usually in sieges, as is well described in accounts of the fifth and seventh Crusades, but it became known as "the calamity of sailors" with the introduction of long voyages, beginning in 1492. Between 1500 and 1800, more seamen died of scurvy than of all other causes combined, including other diseases, shipwreck, accident, and battle.

Vasco da Gama's voyage to the East Indies around the Cape of Good Hope brought death from scurvy to 100 of his 160 sailors. Sir Richard Hawkins of the British Navy said that in his 20 years at sea in the early 17th century, he personally saw about 10,000 mariners perish from scurvy. Through all these vicissitudes, there were as many theories about the causes of scurvy as there were physicians and explorers reporting them: dampness, bad air, poor attitudes, too much blood, constipation, and poor diet.

Scurvy was endemic in cold parts of the world. In one astonishing account, some Norsemen, hard-pressed on a voyage in their long ships, abandoned a shipmate thought to be dying of scurvy on the coast of Greenland. He was unable to walk because of painfully swollen knees. Crawling, he grazed on grass and fully recovered.

Jacques Cartier, the great French sea captain, in 1536 was almost compelled by an outbreak of scurvy to turn back from his famous exploration of the St Lawrence River. He heard, however, that Indians treated this disease with a kind of tea made with the leaves of the "Ameda tree," which was probably spruce. Cartier treated his sailors with the Indian remedy and wrote, "If all the physicians of Louvain and Montpellier had been there with all the drugs of Alexandria, they could not have done as much in a year as that tree did in six days."

In the following century, Captain James Lancaster of the English East India Company set out for India with four ships. One ship was provisioned with lemon juice in bottles because sailors long at sea often had a craving for fresh vegetables and fruits. On the three ships not supplied with lemon juice, 105 of 310 sailors died of scurvy,

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but none on the ship with lemon juice. Neither Captain Lancaster, who was not a doctor, nor the most eminent physicians of the 17th century and even later concluded that lemon juice would prevent scurvy. Many conflicting accounts of what did or did not cure scurvy or prevent it, and many traditional and mistaken theories about the origin of diseases in general—and scurvy in particular—prevented even highly intelligent mariners and physicians from seeing the effects of lemon juice clearly.

As Josh Billings, the 19th century humorist, observed, "It ain't so much what we don't know that holds us back; it's more what we do know that ain't so."

Among the most learned physicians of those days who made important medical discoveries, Herman Boerhave of Leyden, Thomas Willis of Oxford, and Thomas Sydenham of London thought fresh fruits sometimes failed to prevent scurvy. The disease was thought to be due to undiscovered disturbances in the body and vagaries of climate, moisture, cleanliness, infections, or constipation and possibly transmitted by kissing.

Captain James Cook on the first of his famous voyages between 1768 and 1771, exploring New Zealand and Australia, lost a third of his crew to scurvy. On his second voyage, from 1772 to 1775, Cook took great pains to avoid for his seamen various things he had observed to be associated with outbreaks of scurvy. He insisted on cleaner, better ventilated quarters and ample freshwater for personal hygiene for all his men, as well as for the officers. Whenever possible he would take on supplies of whatever fresh fruits, vegetables, and malt were available at ports of call. Cook also noted that scurvy seemed to afflict Dutch sailors less severely than it did the English and concluded that sauerkraut might be a factor. The Dutch were fond of sauerkraut, whereas the English disliked it and ridiculed those who ate it regularly by referring to these wartime enemies as "Krauts." Cook therefore took plenty of sauerkraut aboard, but did not compel his sailors to eat it. He did order his officers to join him in eating sauerkraut daily, encouraging the rest of the crew to follow the officers' example, if they wished to do so. Within a week, every man on the ship was asking for sauerkraut. On that long second voyage, Cook lost only 1 of 118 men to scurvy. He was invited to address the Royal Society of London and was awarded its prestigious Copley Medal—not for preventing scurvy, but rather for his explorations and geographical discoveries. In his address, Cook described all his attentions to the health of his men and expressed the view that even without sauerkraut and fresh fruit, scurvy would have been prevented by cleanliness and freshwater.

James Lind was apprenticed to a physician in Edinburgh at the age of 15 and at 23 joined the British Navy as a ship's surgeon. At the age of 31, having sailed as far as the West Indies, he was convinced from wide reading and mainly astute observation that scurvy had many predisposing causes—among them moist air, weakening by preceding illness such as "gaol fever" (probably a form of typhus), a melancholy disposition, and the hardships of a cold climate. He concluded, however, that there is "an additional and extremely powerful cause . . . which in progress of time . . . seldom fails to breed it. . . . This [cause] is the want of fresh vegetables and greens and ripe fruits." In May of 1747 at sea, he had 12 patients with early signs of scurvy, all of them eating the same regular navy diet, mainly salt pork, biscuits, and a little rum. Two of the 12 sailors he gave, in addition to the regular diet, a quart of apple cider daily. These two were considerably improved after 20 days. Two others he gave 25 drops of vitriol (a kind of metallic mouth wash) three times a day. Their mouths looked a little better, but otherwise there was no improvement. Two others showed no improvement with two teaspoonfuls of vinegar three times a day. Two drank a half pint of seawater daily with no improvement. Two were not improved by small daily doses of nutmeg, garlic, barley water, and tamarind—all prescribed by various physicians for the scurvy. Two of the 12 patients were given two oranges and a lemon daily, and in six days both of them were completely cured.

Lind had conducted the first scientific, controlled experiment in the history of clinical medicine. The results were conclusive, but despite repeated attempts to influence the British Admiralty, he convinced almost no one in the tradition-bound, opinionated network that so many bureaucracies tend to become. Years went by with no action. Lind left the Navy and returned to Edinburgh where he earned his medical degree, in part through the publication of his "Treatise of the Scurvy" in 1753. In this dossier he reviewed the world's literature on the subject and reported the experiments he had done six years earlier. Lind pointed out that few physicians who had not been on long sea voyages could reliably tell scurvy from other diseases. Thus, he observed, physicians claim lemon juice does not cure scurvy because they have been treating other diseases for which lemon juice does no good. On the basis of such failure, German and Hungarian army physicians and "the whole learned college of physicians at Vienna . . . were at a loss how to treat this dreadful calamity" when they saw it.

Glowing admiration for James Lind in recent decades has been challenged by some writers. Why, they ask, did it take 48 years for Lind's original experiment in 1747 to materialize in lemons for the British navy? Perhaps, it is suggested, Lind did not believe strongly in the efficacy of lemons. It is true that he thought there were several "causes" of scurvy. In fact, factors affecting food intake or previous diet and the metabolic demands of other illnesses or hardships in cold weather might have contributed to the susceptibility of various persons to the total or near-total absence of antiscorbutic foods on long voyages. But Lind was clear in identifying "want of fresh vegetables and greens and ripe fruit" as an "extremely powerful cause" of scurvy, and over many years he tried through his writing and through his colleagues and students to persuade the navy to provide lemon juice for sailors. The 48-year delay in changing

British naval policy is not surprising to anyone who has read some of the realistic historical literature, such as Patrick O'Brian's novels about the British navy in Lind's time. The Admiralty in London was not overly concerned with the comfort or diet of sailors, nor inclined toward extra expenditures on them. In general, the Admiralty was disinclined to pay much attention to the opinions of a ship's captain, let alone a ship's surgeon. Some have accused Lind of advocating drinking boiled lemon juice to prevent scurvy. In fact, he reported that boiling lemon juice inactivated its power against scurvy. For a time, he experimented with concentrations by heating well short of boiling, hoping to mitigate the complaint that lemon juice took up too much space in the ship's stores.

Lind's tactful persistence against social and hierarchical odds is one of the reasons to honor him. Nevertheless, despite his great labors and the eloquence of one of his students, Sir Gilbert Blane, it was not until 1795, a year after Lind's death at the age of 78, that the British Admiralty provided an ounce of lemon juice per day at public expense to all its sailors expected to be at sea as long as six weeks. In adopting lemons, the British navy was ahead of all other navies in the world, its own merchant marine, and the British army. It has been estimated that in a single stroke—with lemons—England doubled the size of its effective naval forces.

In 1805 Napoleon was unaware that British seamen were protected from scurvy. He ordered his admirals to lure Nelson's fleet to the West Indies as a feint, believing that by the time they returned to defend against Napoleon's plan to invade England, a great many British sailors would be weakened by scurvy. Nelson did follow some of Admiral Villeneuve's ships to Antigua, but this produced no scurvy on the British ships, whereas 1,000 sick Frenchmen had to be put ashore in Martinique. At Trafalgar, where the French had 46 ships to Nelson's 40, Nelson lost his own life, but Napoleon's fleet was virtually destroyed.

After Trafalgar and during the rest of the 19th century, slow progress was made around the world in preventing and curing scurvy, but nothing was as dramatic as James Lind's posthumous victory. Of special interest is that infantile scurvy was not recognized until the latter half of the 19th century, when bottle-feeding instead of breast-feeding became popular and boiling the milk to prevent newly discovered bacterial diseases greatly reduced or destroyed the vitamin C nature had concentrated in the breast milk of pregnant mammals. Infantile scurvy and its prevention or cure with orange juice was first clearly described by Thomas Barlow of London in 1894, but continued to be debated in learned circles for another decade.

It was not until 1937 that Albert Szent-Györgyi won the Nobel prize for purifying ascorbic acid from Hungarian paprika. Now, of course, scurvy has been virtually eliminated, and some have wryly observed that the highest concentration of vitamin C is in the urine of Americans.

Still, we can recall James Lind's genius, long before there were Nobel prizes, and see its relevance to the daily work of physicians. He was able by careful questioning and the examination of patients to see the important facts in a confusing tangle of contradictory opinions and anecdotes. Lind's story reminds us all that a physician tries "to distinguish in the tumult the beating of the drum."

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Editorials

Pumping Iron

VIRTUALLY EVERY practicing physician who reads this editorial will have now or will have had in the past patients with genetic hemochromatosis in his or her practice. But few will be aware of it.

Embedded in the short arm of chromosome 6, in close physical proximity to the DNA region coding for the HLA histocompatibility complex, lies a gene of unknown function. When both copies of this gene are abnormal, however, dietary iron is absorbed with increased avidity throughout the lifetime of the host—that is, hemochromatosis. It is rare, indeed, that a recessive genetic disorder leads to an increase of a physiologic mechanism, in this case a continued inappropriate absorption of iron in the face of its pathologic accumulation. Until this aberrant gene is finally identified, perhaps by positional cloning, it is unlikely that we shall know how it normally acts to monitor the adequacy of iron stores and thereafter, acting on that information, how it controls the efficiency of iron transport across the intestinal epithelium.

But, then, the normal homeostatic mechanisms for iron metabolism are strange indeed. The level in the body of no other key inorganic substance depends exclusively on the control of absorption. Iron cannot be excreted; it is lost only in small amounts (perhaps 1.0 mg per day) through sloughing of cells or seepage of blood. In the absence of increased bleeding or pregnancy, any daily absorption of more than approximately 1.0 mg will inexorably lead to its accumulation.[1,2]

How does the intestine normally sense the level of iron stores or the rate of erythropoiesis (the other seemingly independent variable in iron absorption)? This remains unknown at present. Does hemochromatosis represent an enhancement of this putative feedback signal? Alternatively, does it represent an intrinsic abnormality in the gut mucosa itself that overrides a normally functioning feedback signaling mechanism? The application of molecular genetics should allow these questions to be answered in the not-too-distant future.

Hemochromatosis represents an overall failure of this gating mechanism in the intestine, such that approximately 2 to 4 mg of iron is absorbed daily. In the absence of bleeding, this is sufficient to increase iron stores by 0.5 to 1.0 gram per year. Over several decades a cumulative pool size characteristic of clinical hemochromatosis (15 to 35 grams) results. Actually, hemochromatosis will undoubtedly prove to be a spectrum of derangements of its miscreant gene when its structure can be specifically analyzed. More than 100 mutations of hemoglobin have been identified. Similarly, we can anticipate that a number of different lesions of the hemochromatotic gene may interfere with its normal function, whatever that might be, and in the process produce wide variations in the resulting peculiar avidity for absorbing dietary iron. Other variables include the level of iron in the diet (normally about 12 to 20 mg per day) and its bioavailability (heme iron is more readily absorbed than free iron). As a result, in a homozygotic patient, sufficient iron to produce the organ damage characteristic of clinical hemochromatosis may accumulate in less than two decades, or never. Most characteristically, this accumulation occurs—or, rather, it is recognized—in the fifth to seventh decades of life. The genetic disease itself is present at birth; its phenotypic expression is long delayed.

How does excessive iron damage the host? Like so many aspects of this common disorder, the answer to that question is still unclear. Evidence suggests that excess iron leads to a peroxidation of key cellular lipids.[3] As an example, cytoplasmic lysosomes contain and sequester powerful hydrolytic enzymes within their lipid membranes. If these membranes are disrupted by peroxidation, however, they may release these enzymes injuriously into the cells' cytoplasm. This is thought to be a major pathogenesis of acute gouty arthritis—that is, the injury of leukocytic lysosomes, in this case by the ingested crystals of monosodium urate. If lysosomal injury is a key, is hemochromatosis a sort of "iron pseudogout" of certain parenchymal organs? The analogy is amusing but not revelatory. Iron overload also diminishes hepatic levels of cytochrome P450 and impairs mitochondrial oxidative metabolism. Some think that excess iron also increases hepatic collagen synthesis in the absence of an overt necrosis of hepatocytes.

Hemochromatosis is one of the most common genetic diseases of whites, exceeding cystic fibrosis in prevalence, for example.[4] Compelling evidence, mostly from the past two decades, strongly supports that conclusion. Approximately 10% of whites carry one abnormal hemochromatotic gene; perhaps 1 person out of every 300 to 400 in the white population is homozygotic for this gene—that is, has genetic hemochromatosis. How has this been established? The data come largely from surveys for biomedical evidence of iron overload in adults (in the absence of other known causes such as transfusions or persistently increased erythropoiesis). Further cases can then be identified in a given family by determining haplotype and allele sharing. Close linkage has been established most frequently with *HLA-A3*, but also with *HLA-B7*, *-B14*, and *-A11*. It is probable that this linkage, representing physical proximity of the genes on chromosome 6, is entirely fortuitous. Nevertheless, before the hemochromatotic gene itself is identified, this guilt by association allows the diagnosis of both heterozygotes and homozygotes to be established in the families of a given index case, even in the absence of iron overload.

Why has hemochromatosis persisted as such a common disorder? Selection pressures might be expected to have diminished its prevalence. On the other hand, clin-

ical manifestations of the disease usually occur after the period of reproduction, although not in the atypical case described elsewhere in this issue of the journal.[5] It has also been postulated that a modest increase in the efficiency of iron absorption in heterozygotes might represent a countervailing positive feature, analogous to the protective effect of heterozygous sickle-cell trait against falciparum malaria.

The clinical manifestations of hemochromatosis vary widely and may be subtle.[1,2] Clearly, physicians must not wait for the appearance of bronzed diabetes with cirrhosis before the diagnosis is considered. If 1 of every 300 to 400 white patients seen in a hospital, clinic, or office has hemochromatosis, the diagnosis is more frequently missed than made. It is true that the full disease does not develop in carriers of the disorder and that women, who are genetically hemochromatotic as frequently as are men, much more rarely accumulate sufficient iron for clinical manifestations to develop (in one study only about 15% of women with genetic hemochromatosis were clinically affected). Menstrual periods and pregnancies allow for substantial iron loss and serve to protect against iron overload. In fact, when clinical hemochromatosis does appear in women, it is usually after menopause. As a result, its manifestations tend to occur later in women than in men.

Weakness, lethargy, abdominal pain, seronegative arthritis, impotence, and glucose intolerance are some of the nonspecific early manifestations of hemochromatosis. How can the diagnosis be made then? The disease must be suspected much more frequently than has been customary in the past. In the absence of a means to detect the abnormal gene itself, we are currently confined to studying the time-delayed phenotypic expression of the disease, that of iron overload. For practical purposes, iron overload (especially greater than 4 grams) in the absence of excessive transfusions, or more rarely, prolonged enhanced erythropoiesis, is almost always due to hemochromatosis. When the diagnosis is made in a patient, it can then be traced in his (more rarely, her) family by HLA linkage analysis. At present, the transferrin saturation test has proved to be the most useful test for detecting iron overload.[6] Other tests are described elsewhere.

Therapy is simple and effective if the diagnosis is made before severe liver disease or the destruction of pancreatic islet beta cells occurs. A hemochromatotic gut slowly but inappropriately pumps iron into the body; a phlebotomist can rapidly pump it out. Removing 500 ml of whole blood removes 200 to 250 mg of iron. Heme itself is the ideal chelator. A weekly phlebotomy can therefore remove 10 to 12 grams of iron per year, which may represent the accumulation of two decades. The genetic defect remains, but its adverse effect can be easily obviated if an early diagnosis is made. Even when the diagnosis is delayed, heart failure and abnormal liver function may be reversed, and even glucose tolerance may improve.

Hemochromatosis is both prevalent and insidious. We must consider this diagnosis much more frequently because genetic "pumping iron" leads to organ destruction, not to body building.

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Advances in Diagnosing and Managing Pituitary Adenomas

IN THE PAST DECADE we have seen a tremendous increase in knowledge regarding the pathogenesis, diagnosis, and management of pituitary tumors, as summarized by Aron and colleagues in this issue of the journal.[1] Their review reflects the experience of a major academic center for pituitary tumor research. What salient points can be gleaned from this experience and from other recent advances?

First, pituitary lesions are not rare. Magnetic resonance (MR) imaging reveals focal pituitary hypointensities in as many as 40% of healthy persons.[2] Most of these are small microadenomas or other benign lesions, but macroadenomas are occasionally found when patients undergo computed tomographic or MR scanning for unrelated indications. How should cases of pituitary mass lesions be evaluated?

To answer this question, it is helpful to review the clinical effects of pituitary adenomas. Pituitary tumors usually present with some combination of three syndromes: symptoms due to the mass itself, symptoms due to a disruption of normal pituitary function, and symptoms due to the oversecretion of pituitary hormones. The first two syndromes depend on the size of the tumor, and the third can occur with small lesions. Therefore, patients with large lesions require formal visual field examination and assessment of normal pituitary function, whereas all patients require assessment of excess hormone secretion.

What is the appropriate biochemical assessment of pituitary function in patients with pituitary mass lesions? There is no single answer to this question, but recent discoveries provide some guidelines:

• *Prolactin oversecretion*: Prolactinomas are the most common pituitary tumor and, in general, are the only ade-

noma type that can be treated medically. Therefore, a serum prolactin measurement should be done in all patients with pituitary mass lesions. Not all patients with hyperprolactinemia and a pituitary tumor have a prolactinoma; any large tumor can cause mild prolactin elevations. *Undersecretion*: Prolactin deficiency is not routinely evaluated or treated.

• *Growth hormone oversecretion*: Some tumors that secrete growth hormone do not cause clinical acromegaly and are mistaken for nonfunctioning tumors.[3] Therefore, a random insulin-like growth factor I (IGF-I) level is helpful in patients with macroadenomas as a marker for excess growth hormone secretion. (IGF-I is produced by the liver under the influence of growth hormone, and its measurement is a better screening test than a random growth hormone level.) *Undersecretion*: Patients are not currently screened for growth hormone deficiency because exogenous growth hormone is not routinely given to adults with a growth hormone deficiency. This recommendation may change, however, depending on results from ongoing trials.[4]

• *Corticotropin (adrenocorticotropic hormone) oversecretion*: A 24-hour urinary free cortisol level is the best screening test for suspected Cushing's syndrome. The further evaluation of such cases is difficult, and patients should be referred to centers where corticotropin-releasing hormone tests and inferior petrosal sinus sampling are available.[5] Most patients with Cushing's disease have microadenomas, and radiologic studies should not be done until the biochemical diagnosis of Cushing's syndrome is assured. *Undersecretion*: If a patient with a macroadenoma is scheduled for a surgical procedure, screening for corticotropin deficiency may not be necessary because the patient will require reexamination postoperatively. If preoperative adrenal insufficiency is suspected, short-term glucocorticoid therapy can be prescribed through the time of the operation. If a surgical procedure is not planned, a corticotropin (cosyntropin [Cortrosyn])-stimulation test can be done to rule out adrenal insufficiency.

• *Thyrotropin (thyroid-stimulating hormone) oversecretion*: Thyrotropin-secreting tumors are rare, and patients with this disorder present with hyperthyroidism. A clue to their presence is a nonsuppressed thyrotropin level (using one of the new sensitive immunometric assays) in a patient with thyrotoxicosis. *Undersecretion*: Free thyroxine (T_4) and thyrotropin levels are sufficient to evaluate the thyroid axis in patients with macroadenomas. Of note, many patients with central hypothyroidism have "normal" thyrotropin levels, although these levels are inappropriate for the low free T_4 levels.[6] Therefore, a thyrotropin level alone can be misleading in evaluating for pituitary tumors.

• *Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) oversecretion*: Until recently, gonadotropin tumors were thought to be rare because they produce no typical clinical syndrome. It is now clear, however, that most clinically nonfunctioning tumors—which constitute 30% of all pituitary adenomas—are in fact gonadotropin-producing.[7] Therefore, in patients with macroadenomas, serum LH and FSH levels should be measured—with a serum testosterone or estradiol level—as tumor markers. *Undersecretion*: Serum LH, FSH, and sex steroid levels are adequate to evaluate the normal gonadal axis in patients with macroadenomas.

• *α-Subunit oversecretion*: Thyrotropin, LH, and FSH are each composed of an α- and a β-subunit. Many pituitary tumors secrete excess amounts of uncombined α-subunit, alone or with other hormones.[7] Although the α-subunit has no bioactivity, it is a helpful tumor marker, and its levels should be measured in patients with macroadenomas. *Undersecretion*: Deficiency of the α-subunit has no clinical effects and does not require evaluation.

Once a patient with a pituitary tumor has been evaluated according to the above guidelines, treatment options must be weighed. Therapy is obviously tailored for each patient, but the following broad guidelines are to be kept in mind:

• *Surgery*: The treatment of choice for most symptomatic pituitary tumors is transsphenoidal surgical excision (with the exception of prolactinomas). Surgical success rates are dependent on surgical skill and experience; the remission rates achieved by Aron and co-workers are difficult to match in community practice. Therefore, patients should be referred to neurosurgeons with an active interest in pituitary tumors.

The issue of remission rates following surgical therapy is especially important for patients with prolactinomas because these tumors can be treated medically. Aron and co-workers report 75% long-term surgical success rates for prolactin microadenomas, with lower success rates for macroadenomas. Other centers report long-term surgical remission rates as low as 40% for prolactin microadenomas and 6% to 29% for macroadenomas.[8-12] Based on these figures, many experts recommend that patients with prolactinomas receive medical, rather than surgical, therapy.

• *Radiation therapy*: Radiation therapy has long been used as primary or adjuvant treatment of pituitary tumors. The gradual development of hypopituitarism is an accepted side effect, but long-term neuropsychiatric effects have not been clarified. Therefore, despite suboptimal surgical cure rates for macroadenomas, many experts withhold postoperative radiation therapy in patients with clinically nonfunctioning tumors. Tumor regrowth may not become a clinical problem within a patient's lifetime, and tumor recurrence can often be treated by repeated transsphenoidal adenomectomy. Radiation therapy remains a useful postoperative treatment of secretory tumors that continue to cause clinical problems due to hormone excess.

• *Medical therapy*: Medical therapy for pituitary tumors, nonexistent 20 years ago, is now commonplace for the following tumor types:

Prolactinomas. In the view of many experts, the dopamine agonist bromocriptine hydrochloride is the treatment of choice for prolactinomas of any size. In most

patients, bromocriptine therapy decreases serum prolactin levels, improves pituitary function, and reduces tumor size, with none of the side effects of surgical therapy.[13] The optimal duration of bromocriptine treatment is unclear. Some women with microadenomas have remission of hyperprolactinemia, so therapy can be discontinued in these patients after one or two years, with close monitoring for recurrence.[14] In contrast, most patients with macroadenomas require permanent bromocriptine therapy.[15]

What are the medical options for patients who are not helped by bromocriptine therapy?[13] Other dopamine agonists may be effective; pergolide mesylate is marketed in the United States (although not approved for the treatment of prolactinomas), but other dopamine agonists are in clinical trials. Vaginal bromocriptine administration is an option for women who have side effects with oral bromocriptine. Finally, women with prolactin microadenomas who do not desire fertility can safely receive oral contraceptives or estrogen replacement therapy, which treat the estrogen-deficiency state without causing tumor growth.[16]

Acromegaly. The use of the somatostatin analogue octreotide decreases growth hormone levels in most patients with acromegaly. But it causes tumor shrinkage in only a few patients. Therefore, it is most useful in patients who cannot undergo a surgical procedure or who have persistent disease postoperatively.

Cushing's disease. As reviewed by Aron and coworkers, the results of the medical treatment of Cushing's disease remain disappointing.

Thyrotropin-secreting tumors. Octreotide is useful as adjuvant therapy for reducing excess thyrotropin secretion, although its effects on tumor size are variable.

Gonadotropin and α-subunit tumors. Currently no effective medical therapy is available for these tumors. Recent trials suggest, however, that the administration of gonadotropin-releasing hormone antagonists may prove useful as adjuvant therapy.[17]

• *Observation*: Patients with nonfunctioning microadenomas can be observed without therapy, with follow-up scanning to rule out tumor growth. Patients with nonfunctioning macroadenomas should undergo surgical resection or, if completely asymptomatic, should be observed closely with scanning.[18]

Finally, what can recent advances in molecular biology teach us about the pathogenesis of pituitary adenomas? Although molecular studies suggest that pituitary adenomas are monoclonal in origin, specific genetic abnormalities have been identified only in a few tumors. A loss of chromosome sequences that contain the putative *MEN1* tumor suppressor gene has been reported in a subset of growth hormone-secreting adenomas, whereas activating mutations in the *Gs* α-subunit gene have been found in various functioning and nonfunctioning adenomas.[19] Future studies of such genetic alterations may present new opportunities for the diagnosis and treatment of pituitary tumors.

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Lessons From the Practice

The Healing Touch

JOE VANDER VEER Jr, MD, *Phoenix, Arizona*

For centuries, the healing touch was perhaps the most valuable arrow in the therapeutic quiver, epitomized so effectively in Sir Luke Fildes's painting of "The Doctor," where the reflective, caring, and doubtless exhausted physician is taking the pulse of a sick child during a home visit, perhaps awaiting the crisis of some infectious disease while the apprehensive parents cower in the shadows.

We may think that the laying on of hands is passé or belongs in some religious context in this era of highly technical medicine. What does the human touch have to offer today, when we rely so heavily on computed tomography, magnetic resonance imaging, and sophisticated serum tests? It offers a lot. It is an expectation that many patients have from an encounter with their physician. It is part of an adequate evaluation, the time-honored "history and physical." In that context, it may be one of the best ways physicians have to let patients know they know their stuff. It is a great way to establish rapport.

In no other professional encounter do persons allow another access to their body—not when you see your lawyer or your pastor about a problem do you let yourself be so vulnerable and exposed. It cuts both ways, obviously, as complaints about sexual advances by physicians bear out. But, used correctly, the healing touch can produce trust and confidence.

That was brought home to me when working as an emergency physician. I began to extend the "90-second trauma examination" to nontrauma patients as a quick check. I was struck by the number of patients who commented that they had not been examined before like that. They seemed impressed by my thoroughness, and I thought that they heeded my recommendations better for it. The suggestion of the quick miniphysical examination became part of my teaching to residents in our program.

I have been impressed with touching the patient as a means of conveying caring. Francis Peabody put it best in 1927: "The secret of the care of the patient is in caring for the patient" ("The care of the patient." *Journal of the American Medical Association* 1927; 88:877-882). It is one of the secrets of the bedside manner to sit down, to inquire, to look and listen, and to touch the patient, conveying concern and caring. We need, perhaps today more than ever, the healing human touch.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Vander Veer J Jr: The healing touch. West J Med 1995; 162:374)

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Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

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Mass Circulation Publications **(Do not include in reference list; put in text)**

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee,* September 8, 1985, p 5)

Personal Communications and Unpublished Data

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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ARIZONA

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 19-23—**Women's Health**. American Academy of Family Physicians at The Buttes, Tempe. Wed-Sun. Contact: (800) 926-6890, ext 5245.

April 20-22—**5th Annual Advances and Controversies in Clinical Nutrition**. Mayo Clinic/Mayo Foundation, Phoenix. Thurs-Sat. Contact: (800) 462-9633.

April 22—**Fifth Annual Arizona HPV and Cervical Cancer Conference: New Approaches.** Scottsdale Memorial Hospital. Sat. Contact: Diane, (602) 994-8330.

May 7-11—**Fundamental Principles of Pharmacokinetics and Toxicokinetics for the Industrial Scientist.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Sun-Thurs. Contact: Lynne Mascarella, U of A.

May 24-27—**28th Annual Conference: Suicide Update 1995: What We Know and Where We Need to Go.** American Association of Suicidology at the Arizona Biltmore, Phoenix. Wed-Sat. Contact: Patricia J. Horgas, RN, (202) 237-2280.

June 23-25—**18th Annual Pediatrics in the Red Rocks**. American Academy of Pediatrics, Arizona Chapter, and Maricopa Medical Center at Los Abrigados Resort, Sedona. Fri-Sun. Contact: Melanye Wrighton. (602) 230-1949.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix. AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

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ANESTHESIOLOGY

May 18-21—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $350. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691

May 19-21—**42nd Annual Meeting of the Association of University Anesthesiologists.** UCSD at Hyatt Regency, San Diego. Fri-Sun. 17 hrs. $400. Contact: UCSD.

May 21-26—**UCSD Anesthesiology Review Course**. UCSD at San Diego Princess. Sun-Fri. 37.5 hrs. $500. Contact: UCSD.

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $285. Contact: CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

CARDIOLOGY

April 28-30—**Arrhythmias: Interpretation, Diagnosis and Management**. Medical Education Resources at Sheraton Desert Inn, Las Vegas. Fri-Sun. 11 hrs. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

May 11-13—**5th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 12—**Stress Echo: Meet the Experts**. Hospital of the Good Samaritan. Fri. Contact: Charles Pollick, (213) 977-2335

DERMATOLOGY

June 9-11—**3rd Annual Skin Rejuvenation Seminar**. Medical Education Resources at Cosmetic Surgery Group of Newport Beach. Fri-Sun. 19 hrs. $2200. Contact: Martin Borsanyi, c/o The Professional Image, (714) 760-1522

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 14-17—**3rd International Symposium on Cutaneous Fungal, Bacterial, and Viral Infection and Therapy**. UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sun. 24 hrs. $395. Contact: UCSF.

EMERGENCY MEDICINE

May 8-12—**Emergency Medicine Symposium I**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 16-17—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians at San Francisco. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

June 19-23—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-21—**High Risk Emergency Medicine and Acute Care**. American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

July 26-30—**Wilderness Medicine 1995**. American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $495. Contact: Jackie Silva, 1908 Ashland St. Ste A, Ashland, OR 97520. (800) 888-5632.

August 6-10—**5th National Emergency Medicine Conference: Staying Alive in '95**. Kaiser Permanente at Ritz-Carlton, Kapalua, Maui, Hawaii. Sun-Thurs. 34 hrs. Contact: Joseph Federl, Two Harrison St, #140, San Francisco 94105. (800) 782-4554.

(Continued from Page 377)

August 23-24—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians and Emergency Physicians' Medical Group at Pan Pacific Hotel, San Diego. Wed-Thurs. 15 hrs. $295-$495. Contact: Alpen Meeting Service, (800) 451-7475.

EPIDEMIOLOGY/INFECTIOUS DISEASE

September 22-24—**HIV, AIDS and Women.** UCSD at La Jolla Marriott, La Jolla. Fri-Sun. 18 hrs. $175. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

April 27-30—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

May 10-13—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

May 12-13—**Primary Care for the 90s.** University of Nevada School of Medicine at Hyatt Regency at Lake Tahoe, Incline Village, Nevada. Fri-Sat. 11 hrs. $250. Contact: Continuing Education, Manville Bldg/342, UNSM, NV 89557. (702) 784-4605.

May 20—**Gynecology for Primary Care**. UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. Contact: UCD.

June 11-16—**19th Annual Fingers to the Toes: Orthopaedics for Primary Care**. UCD at Stanford Sieraa Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. Contact: UCD.

July 7-9—**39th Annual Postgraduate Symposium of the San Diego Academy of Family Physicians.** Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-300. Contact: Terry Camarata, PO Box 5996, Chula Vista 91912. (619) 422-1186.

July 10-13—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425. Contact: UCSF.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 379)

UCSF

CME CALENDER

1995 Continuing Medical Education Programs Presented by the Department of Medicine, **University of California, San Francisco,** School of Medicine.

For Further infomation, or a more detailed program brochure, contact the Deparment of Medicine Postgraduate Programs Office at 415.476.5208 or FAX them at 415.476.3542.

Sponsored by the University of California School of Medicine at San Francisco Office of Continuing Medical Education. CME Credits vary per course.

Topic	Date	Location
Primary Care Cardiology	April 1	ANA Hotel, San Francisco
Advances in Emergency Medicine	April 5-8	Ritz-Carlton, San Francisco
Primary Care Update	April 16-21	Inter-Continental Hotel, Maui, Hawaii
Advances in Infectious Diseases	April 26-28	Fairmont Hotel, San Francisco
Advances in Internal Medicine	May 22-26	Ritz-Carlton, San Francisco
Advances in Internal Medicine	June 19-23	UCSF Campus, San Francisco
Critical Care Cardiology	August 10-12	Ritz-Carlton, San Francisco
Essentials of Primary Care	August 20-25	Squaw Valley, California
Clinical Care of the AIDS Patient	August 24-29	Sun Valley, Idaho
Design and Methods of Clinical Trials	September 14-15	Sir Francis Drake, San Francisco
Gastroenterology	September 29-October 1	ANA Hotel, San Francisco
Cardiology Update	October 5-7	Carmel Valley Resort, California

CONTINUING MEDICAL EDUCATION

(Continued from Page 378)

August 4-6—**Cardiology for the Family Physician and Internist**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 7-9—**Dermatology for the Non-Dermatologists**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Primary Care Medicine: A Practical Approach**. Scripps Clinic and Research Foundation at Le Meridien San Diego at Coronado. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 21-23—**Sports Medicine and Industrial Medicine for Primary Care Physicians**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASE

April 26-28—**16th Annual Advances in Infectious Dieseases**. UCSF at Fairmont Hotel, San Francisco. Wed-Fri. 16 hrs. $410. Contact: UCSF.

June 7—**9th Annual AIDS Conference: Challenge for Today—Hope for Tomorrow.** Alta Bates Medical Center at Mills College, Oakland. Wed. 7 hrs. Contact: Caroline Carey, (510) 204-3884.

INTERNAL MEDICINE

May 22-26—**23rd Annual Advances in Internal Medicine**. UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 33 hrs. $645. Contact: UCSF.

OCCUPATIONAL/ENVIRONMENTAL

April 28-May 5—**American Occupational Health Conference.** American College of Occupational and Environmental Medicine at Sands Expo and Convention Center, Las Vegas. Fri-Fri. Contact: ACOEM, 55 W Seegers Rd, Arlington Heights, IL 60005. (708) 228-6850.

ONCOLOGY

June 4—**Lymphoproliferative Disorders.** California Tumor Tissue Registry at Westin South Coast Plaza, Costa Mesa. Sun. 8 hrs. Contact: Anne Chism, CTTR, 11021 Campus Ave, AH 335, Loma Linda 92350. (909) 824-4788.

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

May 6—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 1-2—**Annual Ophthalmology Symposium**. UCD at Vizcaya, Sacramento. Thurs-Fri. Contact: UCD.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

ORTHOPEDICS

May 18-21—**10th Annual Symposium of the Spine Study Group**. Spine Study Group at Westin Mission Hills, Rancho Mirage. Thurs-Sun. Contact: Pat Curl, Meeting Coordinator, 4805 Mercury St, Ste E, San Diego 92111. (619) 279-9955.

OTOLARYNGOLOGY

May 7-12, June 4-9—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

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(inside California)
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San Francisco, CA 94105

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June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach**. UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

November 2-4—**San Francisco Otology-Neurotology—1995.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 24 hrs. Contact: UCSF.

PATHOLOGY

May 25-27—**Current Issues in Anatomic Pathology: 1995**. UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF

August 12-19—**16th Annual Comprehensive Fine Needle Biopsy Course**. UCSF at Ritz-Carlton, San Francisco. 1 wk. 27 hrs. $950. Contact: UCSF.

PEDIATRICS

May 4-6—**28th Annual Advances and Controversies in Clinical Pediatrics**. UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

July 21-22—**3rd Annual Pediatrics Update**. Stanford University at Lucile Packard Children's Hospital. Fri-Sat. Contact: Elinor Meyer, Continuing Medical Education, 725 Welch Road, Palo Alto 94304. (415) 497-8554.

PSYCHIATRY AND NEUROLOGY

May 6-7, May 20-21—**32nd Annual Basic Workshop in Clinical Hypnosis.** San Francisco Academy of Hypnosis at Alta Bates Medical Center, Berkeley. Sat-Sun. $250. Contact: Jan Brooks, SFAH-ERF, 615 27th St, San Francisco 94131. (415) 282-3399.

(Continued on Page 380)

CSIM's 1995 Annual Meeting

Don't miss the celebration! Join us in the City by the Bay for CSIM's 50th Annual Meeting at the Grand Hyatt on Union Square. Network with other internists, earn up to six (6) Category I CME credits, and get the latest in clinical and socioeconomic information relating to internal medicine. Bring your family and friends and experience San Francisco. Courses include:

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- ★ A Delicate Balance: Primary and Specialty Internists Under Managed Care

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CONTINUING MEDICAL EDUCATION

(Continued from Page 379)

May 24-26—**14th Annual Child Abuse and Neglect Conference**. UCD at Red Lion Hotel, Sacramento. Wed-Fri. 15 hrs. Contact: UCD.

July 25-30—**Neuropsychiatric Emergencies and Crisis Update and Review**. Southern California Neuropsychiatric Institute at Mauna Kea, Hapuna Beach Hotel, Hawaii. Tues-Sun. Contact: Ann McCormick, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102

RADIOLOGY

July 16-20—**Advanced Imaging of the Spine**. UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 24 hrs. $550. Contact: UCSD.

SURGERY

April 29-30—**Endoscopic Plastic Surgery and Beyond.** UCSD at UCSD BSB and Thornton Hospital, La Jolla. Sat-Sun. 13 hrs. $1250. Contact: UCSD.

May 14-17—**36th Annual Meeting: Society for Surgery of the Alimentary Tract**. UCSD at San Diego Convention Center. Sun-Wed. 23 hrs. Contact: UCSD.

June 14-17—**12th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency, La Jolla. Wed-Sat. Contact: Rebecca Quiring, 3905 Waring Road, Oceanside 92056. (619) 940-2066.

July 3-6—**Aesthetic Plastic Surgery of the Face, Eyes, Nose and Neck.** International Surgical Society at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. 19 hrs. $700. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 381)

MEMORIAL/UCI CENTER FOR HEALTH EDUCATION

APRIL, 1995

Advanced Urogynecology and Pelvic Surgery
April 5-9, 1995
MARQUIS HOTEL AND VILLAS
PALM SPRINGS, CALIFORNIA

4th Annual OB/GYN Ultrasound—The State of the Art
April 11-14, 1995
WESTIN RESORT
MAUI, HAWAII

20th Annual Care of the Sick Newborn Symposium
April 26-28, 1995
HYATT REGENCY HOTEL
LONG BEACH, CALIFORNIA

MAY, 1995

6th Annual Philip J. DiSaia Society—OB/GYN Symposium
May 19, 1995
DOUBLETREE HOTEL
ORANGE, CALIFORNIA

JUNE, 1995

UCI Family Practice Refresher Course
June 12-17, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

JULY, 1995

4th Annual Internal Medicine Board Review Course
July 31-August 4, 1995
LE MERIDIEN HOTEL
NEWPORT BEACH, CALIFORNIA

AUGUST, 1995

13th Annual Controversies in Obstetrics and Gynecology
August 2-5, 1995
HAPUNA BEACH PRINCE HOTEL
MAUNA KEA RESORT
ISLAND OF HAWAII

SEPTEMBER, 1995

3rd International Symposium on the Difficult Airway
September 15-17, 1995
SUTTON PLACE HOTEL
NEWPORT BEACH, CALIFORNIA

OCTOBER, 1995

18th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecologic Histopathology
October 23-28, 1995
WESTIN SOUTH COAST PLAZA HOTEL
COSTA MESA, CALIFORNIA

NOVEMBER, 1995

6th Annual Practical Methods of Diabetes Management
November 3-4, 1995
SUTTON PLACE HOTEL
NEWPORT BEACH, CALIFORNIA

Current Issues in Perinatal Medicine
November 10-12, 1995
MARRIOTT'S RANCHO LAS PALMAS RESORT
RANCHO MIRAGE, CALIFORNIA

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CME CREDITS VARY PER COURSE.

(Continued from Page 380)

GENERAL/MULTIDISCIPLINARY

April 28—**The Cutting Edge 1995: How to Treat Difficult Patient.** UCSD at Pan Pacific Hotel, San Diego. Fri. 13 hrs. $325. Contact: UCSD.

May 6-7—**Clinical Practice Guidelines in Long-Term Care.** California Association of Medical Directors at Pan Pacific Hotel. Anaheim. Sat-Sun. 12.5 hrs. $185. Contact: CAMD, 1721 2nd St, #101. Sacramento 95814. (916) 556-3355.

June 2-4—**8th Annual Medical Office Laboratory.** San Diego State University at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $475. Contact: Nanacy Geiser, College of Extended Studies, (619) 594-6255.

June 23—**The Future of American Medicine: A Bioethics Symposium.** UCD at Cancer Center Auditorium. Fri. 3 hrs. Contact: UCD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 24-28—**Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center, Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 28-August 1—**80th Annual Summer Conference.** Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center. Wheat Ridge. Contact: Jean A. Kline. (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave. Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Medical Education, Primary Children's Medical Center, Salt Lake City, at Sun Valley Resort, Sun Valley. Fri-Sun. Contact: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City, UT 84113. (801) 588-2000.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 22—**New Mexico Society of Anesthesiologists—Annual Meeting.** Hilton Hotel of Santa Fe. Sat. Contact: Robin Clifton, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

May 11-13—**New Mexico Medical Society Annual Meeting.** New Mexico Medical Society, Albuquerque. Thurs-Fri. Contact: Robin Clifton, 7770 Jefferson NE, Ste, 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Fri-Sat.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals. Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

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UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

May 26-28—**20th Annual Conference on Neonatal/Perinatal Medicine.** The Center for Pediatric Continuing Education at the Cliff Lodge at Snowbird. Fri-Sun. Contact: PCMC.

June 7-10—**1995 Summer Pediatric Neurosurgery Symposium.** University of Utah School of Medicine at Stein Eriksen Lodge in Deer Valley, Park City. Wed-Sat. Contact: UUSM.

June 19-21—**17th Annual Conference on Common Problems in Pediatrics.** The Center for Pediatric Continuing Education at the University Park Hotel, Salt Lake City. Mon.-Wed. Contact: PCMC.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Education at Sun Valley Resort, Sun Valley, Idaho. Fri-Sun. Contact: PCMC.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 5-6—**Mental Health Update.** U/W. Fri-Sat. Contact: U/W.

May 20-21—**PALS**. Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

June 1-3—**Primary Care Update of OB-GYNs.** Seattle. Thurs-Sat. Contact: U/W.

June 2-3—**6th Update on Travel and International Medicine**. Seattle. Fri-Sat. Contact: U/W.

June 7-10—**Bariatric Medicine**. Seattle. Wed-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 8-10—**Wyoming Medical Society—Annual Meeting**. Jackson Lake Lodge, Moran. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

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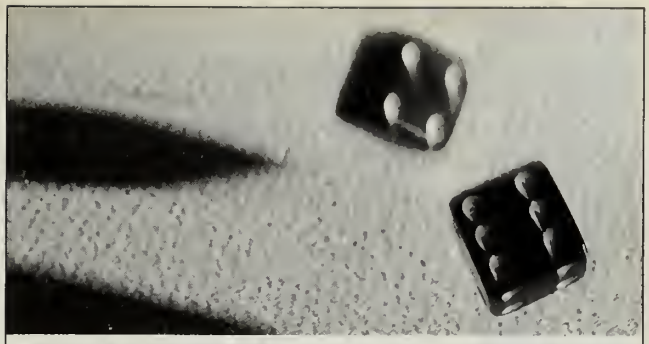

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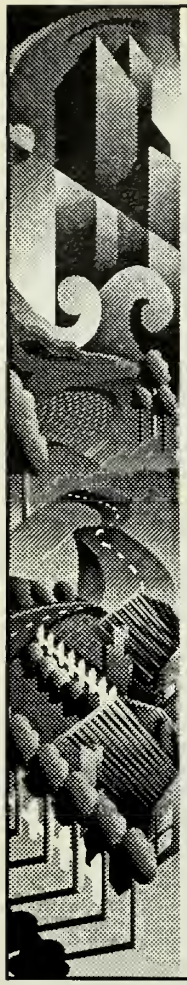

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Send or fax your CV to Julie Guzman, Physician Resources Coordinator, San Jose Medical Group, Inc.,* 45 S. 17th St., San Jose, CA 95112, or call (408) 282-7833. Fax (408) 297-0939.

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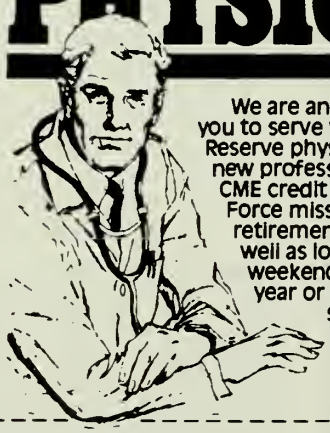

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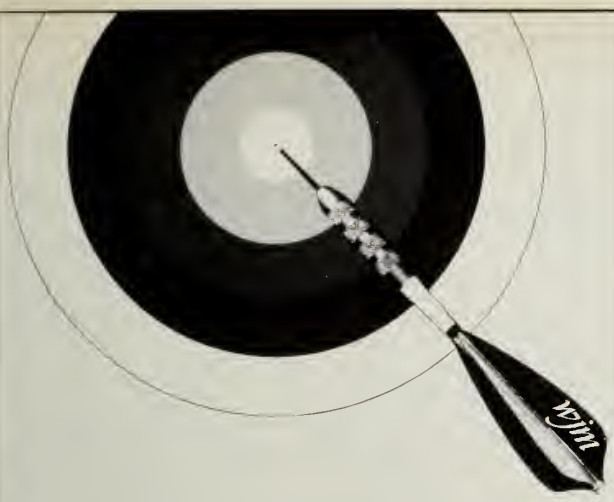

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ABSTRACTS MAY 1995

(Cherington M, Yarnell PR, London SF: Neurologic complications of lightning injuries. West J Med 1995; 162:413-417)

Over the past ten years, we have cared for 13 patients who suffered serious neurologic complications after being struck by lightning. The spectrum of neurologic lesions includes the entire neuraxis from the cerebral hemispheres to the peripheral nerves. We describe these various neurologic disorders with regard to the site of the lesion, severity of the deficit, and the outcome. Damage to the nervous system can be a serious problem for patients struck by lightning. Fatalities are associated with hypoxic encephalopathy in patients who suffered cardiac arrests. Patients with spinal cord lesions are likely to have permanent sequelae and paralysis. New technology for detecting lightning with wideband magnetic direction finders is useful in establishing lightning-flash densities in each state. Florida and the Gulf Coast states have the highest densities. Colorado and the Rocky Mountain states have the next highest.

LIGHTNING INJURIES
LIGHTNING DEATHS
ELECTROCUTION
LIGHTNING-FLASH DENSITY

(Cherington M, Yarnell PR, London SF: Neurologic complications of lightning injuries. West J Med 1995; 162:413-417

Over the past ten years, we have cared for 13 patients who suffered serious neurologic complications after being struck by lightning. The spectrum of neurologic lesions includes the entire neuraxis from the cerebral hemispheres to the peripheral nerves. We describe these various neurologic disorders with regard to the site of the lesion, severity of the deficit, and the outcome. Damage to the nervous system can be a serious problem for patients struck by lightning. Fatalities are associated with hypoxic encephalopathy in patients who suffered cardiac arrests. Patients with spinal cord lesions are likely to have permanent sequelae and paralysis. New technology for detecting lightning with wideband magnetic direction finders is useful in establishing lightning-flash densities in each state. Florida and the Gulf Coast states have the highest densities. Colorado and the Rocky Mountain states have the next highest.

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LIGHTNING INJURIES
LIGHTNING DEATHS
ELECTROCUTION
LIGHTNING-FLASH DENSITY

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

In Memoriam

California Medical Association

Bloomenthal, Ernest D., La Jolla. Died Jan 2, 1995, aged 89. Graduate of Northwestern University School of Medicine, Chicago, Illinois, 1935. Licensed in California in 1964. Dr Bloomenthal was a member of the San Diego County Medical Society.

Brinckerhoff, Elmer E., Oakland. Died Dec 1994, aged 74. Graduate of Stanford University School of Medicine, Stanford, California, 1946. Licensed in California in 1946. Dr Brinckerhoff was a member of the Alameda-Contra Costa Medical Association.

Bundy, Robert P., San Lorenzo. Died Jan 15, 1995, aged 74. Graduate of University of California, Irvine, 1962. Licensed in California in 1962. Dr Bundy was a member of the Alameda-Contra Costa Medical Association.

Calverley, Roderick K., Borrego Springs. Died Apr 2, 1995, aged 56. Graduate of University of British Columbia Faculty of Medicine, Vancouver, 1962. Licensed in California in 1972. Dr Calverley was a member of the San Diego County Medical Society.

Chamberlain, Francis L., San Francisco. Died Feb 25, 1995, aged 89. Graduate of University of California, San Francisco, School of Medicine, 1934. Licensed in California in 1934. Dr Chamberlain was a member of the San Francisco Medical Society.

Christie, Ivan T., Watsonville. Died Mar 22, 1995, aged 72. Graduate of University of Vienna, Austria, 1947. Licensed in California in 1953. Dr Christie was a member of the Santa Cruz County Medical Society.

Dalton, Edward B., Monterey. Died Mar 29, 1995, aged 58. Graduate of Wayne State University School of Medicine, Detroit, Michigan, 1961. Licensed in California in 1967. Dr Dalton was a member of the Monterey County Medical Society.

Elzey, Neil D., Sacramento. Died Feb 27, 1995, aged 78. Graduate of University of California, San Francisco, School of Medicine, 1942. Licensed in California in 1942. Dr Elzey was a member of the Sacramento-El Dorado Medical Society.

Feinstein, Myron S., Redwood City. Died Mar 5, 1995, aged 72. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1945. Licensed in 1950. Dr Feinstein was a member of the San Mateo County Medical Association.

Hardy, George C. Jr, Sacramento. Died Mar 3, 1995, aged 56. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1962. Licensed in California in 1972. Dr Hardy was a member of the Sacramento-El Dorado Medical Society.

Hippen, Robert L., San Diego. Died Mar 14, 1995, aged 76. Graduate of University of Tennessee Center for Health Science, Memphis, 1945. Licensed in California in 1946. Dr Hippen was a member of the San Diego County Medical Society.

Klinefelter, James A., Sacramento. Died Mar 10, 1995, aged 88. Graduate of Stanford University School of Medicine, Stanford, California, 1937. Licensed in California in 1937. Dr Klinefelter was a member of the Sacramento-El Dorado Medical Society.

Kremser, Elisabeth., Walnut Creek. Died Jan 19, 1995, aged 73. Graduate of University of California, San Francisco, School of Medicine, 1945. Licensed in California in 1945. Dr Kremser was a member of the Alameda-Contra Costa Medical Association.

Madeley, H. Randall, Vallejo. Died Mar 4, 1995, aged 86. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1934. Licensed in California in 1938. Dr Madeley was a member of the Solano County Medical Society.

May, Angelo, San Francisco. Died Mar 3, 1995, aged 82. Graduate of George Washington University School of Medicine, Washington, DC. Licensed in California in 1939. Dr May was a member of the San Francisco Medical Society.

Miller, J. Randall, Chula Vista. Died Mar 16, 1995, aged 53. Graduate of Northwestern University School of Medicine, Chicago, Illinois, 1966. Licensed in California in 1971. Dr Miller was a member of the San Diego County Medical Society.

St Hill, Clyde Randolph, San Diego. Died Apr 1995, aged 49. Graduate of University of California, San Diego, School of Medicine, La Jolla, 1974. Licensed in California in 1978. Dr St Hill was a member of the San Diego County Medical Society.

Scheidt, John E., Dana Point. Died Mar 2, 1995, aged 83. Graduate of Ohio State University, 1943. Licensed in California in 1949. Dr Scheidt was a member of the Orange County Medical Association.

Sibley, Wixom S., Redwood City. Died Feb 1995, aged 82. Graduate of University of Michigan Medical School, Ann Arbor, 1936. Licensed in California in 1940. Dr Sibley was a member of the San Mateo County Medical Association.

Vicencio, Deogracias D., La Habra. Died Dec 4, 1994, aged 69. Graduate of University of Santo Tomas, Manila, 1955. Licensed in California in 1972. Dr Vicencio was a member of the Orange County Medical Association.

Wall, Charles V., Victorville. Died Feb 1995, aged 64. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Wall was a member of the Orange County Medical Association.

New Mexico Medical Society

Evans, Junius A., Roswell. Died Apr 4, 1995, aged 84. Graduate of University of Texas Medical School, 1943. Licensed in New Mexico in 1947. Dr Evans was a member of the Chaves County Medical Society.

Hunter, William M., Albuquerque. Died Feb 4, 1995, aged 70. Graduate of Liverpool Faculty of Medicine, England, 1949. Licensed in New Mexico in 1981. Dr Hunter was a member of the Greater Albuquerque Medical Association.

Wang, Basil L., Belen. Died Dec 20, 1994, aged 83. Graduate of Buy's Hospital, London University, England, 1934. Licensed in New Mexico in 1954. Dr Belen was a member of the Valencia County Medical Society.

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"I am proud of our profession, and I am proud of the AMA."

Lonnie R. Bristow M.D.

Member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

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Dr Nathan is Director, the Diabetes Research Center, Diabetes Clinic, and Mallinckrodt General Clinical Research Center, Massachusetts General Hospital, and Associate Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

May 24-27—**28th Annual Conference: Suicide Update 1995: What We Know and Where We Need to Go.** American Association of Suicidology at the Arizona Biltmore, Phoenix. Wed-Sat. Contact: Patricia J. Horgas, RN, (202) 237-2280.

June 3—**Vulnerabilities of Psychologists as Expert Witnesses.** U of A at the Ritz Carlton Hotel, Phoenix. Sat. Contact: U of A.

June 14—**Obstetrical Practice: Avoiding Liability.** Mutual Insurance Company of Arizona at the Westin La Paloma, Tucson. Wed. Contact: Shawn Fleishon, (602) 956-5276 or (800) 352-0402.

June 23-25—**18th Annual Pediatrics in the Red Rocks**. American Academy of Pediatrics, Arizona Chapter, and Maricopa Medical Center at Los Abrigados Resort, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

July 21-22—**Clinical Update: Practical Medicine for the Primary Care Physician**. U of A and NAAHEC at Little America, Flagstaff. Fri-Sat. Contact: Rose Howe, (502) 774-6687.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

June 9-10—**Clinical Management of Asthma and Allergic Disease**. Medical Education Resources at Parc 55 Hotel, San Francisco. Fri-Sat. 8.5 hrs. Contact: Linda Main, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

September 30—**Contemporary Management of Sinusitis**. UCSF at Laurel Heights Auditorium, San Francisco. Sat. Contact: UCSF.

ANESTHESIOLOGY

May 18-21—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $350. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691

May 19-21—**42nd Annual Meeting of the Association of University Anesthesiologists.** UCSD at Hyatt Regency, San Diego. Fri-Sun. 17 hrs. $400. Contact: UCSD.

May 21-26—**UCSD Anesthesiology Review Course**. UCSD at San Diego Princess. Sun-Fri. 37.5 hrs. $500. Contact: UCSD.

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $285. Contact: CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

October 29-November 4—**Hawaiian Seminar on Clinical Anesthesia**. California Society of Anesthesiologists at Hyatt Regency Poipu Beach, Kauai, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

DERMATOLOGY

June 9-11—**3rd Annual Skin Rejuvenation Seminar**. Medical Education Resources at Cosmetic Surgery Group of Newport Beach. Fri-Sun. 19 hrs. $2200. Contact: Martin Borsanyi, c/o The Professional Image, (714) 760-1522

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 14-17—**3rd International Symposium on Cutaneous Fungal, Bacterial, and Viral Infection and Therapy**. UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sun. 24 hrs. $395. Contact: UCSF.

EMERGENCY MEDICINE

June 19-23—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20-21—**High Risk Emergency Medicine and Acute Care**. American College of Emergency Physicians at Las Vegas, Nevada. Tues-Wed. 15 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 452-7475.

July 26-30—**Wilderness Medicine 1995**. American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

August 6-10—**5th National Emergency Medicine Conference: Staying Alive in '95**. Kaiser Permanente at Ritz-Carlton, Kapalua, Maui, Hawaii. Sun-Thurs. 34 hrs. Contact: Joseph Federl, Two Harrison St, #140, San Francisco 94105. (800) 782-4554.

August 23-24—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians and Emergency Physicians' Medical Group at Pan Pacific Hotel, San Diego. Wed-Thurs. 15 hrs. $295-$495. Contact: Alpen Meeting Service, (800) 451-7475.

September 22—**Advanced Burn Life Support.** Torrance Memorial Medical Center. Fri. 9 hrs. $220. Contact: Nancy Wise, Torrance Memorial Burn Center, 3330 Lomita Blvd, Torrance 90505. (310) 517-4605, ext. 7607.

CONTINUING MEDICAL EDUCATION

October 13-15—**Advances in Emergency Medicine.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

September 22-24—**HIV, AIDS and Women.** UCSD at La Jolla Marriott, La Jolla. Fri-Sun. 18 hrs. $175. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

June 3—**Primary Health Care for the Older Woman.** UCSF/Mount Zion Center on Aging. Sat. Contact: Mary Henderson, (415) 750-4170.

June 11-16—**19th Annual Fingers to the Toes: Orthopaedics for Primary Care.** UCD at Stanford Sieraa Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. Contact: UCD.

June 23—**4th Ambulatory Health Care Accreditation Conference.** California Medical Association's Ambulatory Care Review Committee at San Francisco. Fri. 3 hrs. Contact: Pat Ferrigno, 221 Main St, P O Box 7690, San Francisco 94120-7690. (415) 882-5168.

July 7-9—**39th Annual Postgraduate Symposium of the San Diego Academy of Family Physicians.** Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-300. Contact: Terry Camarata, PO Box 5996, Chula Vista 91912. (619) 422-1186.

July 10-13—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425. Contact: UCSF.

July 14-16—**Neurology for the Non-Neurologist.** Medical Education Resources at Silverado Resort, Napa Valley. Fri-Sun. 11 hrs. Contact: Linda Main, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

July 21-23—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs. Contact: Linda Main, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 4-6—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 7-9—**Dermatology for the Non-Dermatologists.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien San Diego at Coronado. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 21-23—**Sports Medicine and Industrial Medicine for Primary Care Physicians.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 16-18—**Radiology for the Non-Radiologist.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 25-28—**Wound Management Workshop for Primary Care Professionals.** UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

October 26-29—**Nevada Academy of Family Physicians.** NAFP at Tropicana Hotel, Las Vegas, Nevada. Thurs-Sun. 21 hrs. Contact: Barbara Bollin, NAFP, P O Box 27713, Las Vegas, NV, 89126-1713. (702) 647-0117.

INFECTIOUS DISEASE

June 7—**9th Annual AIDS Conference: Challenge for Today—Hope for Tomorrow.** Alta Bates Medical Center at Mills College, Oakland. Wed. 7 hrs. Contact: Caroline Carey, (510) 204-3884.

(Continued on Page 406)

Report on Financing of Practice Acquisitions

HPSC Financial Services has recently provided the financing for the acquisition of practices whose selling prices are shown below.

State Selling Price	State Selling Price	State Selling Price
CA . . $60,000	GA . $329,000	MI. . $365,000
CA . . . 55,000	ID . . . 225,000	MI. . . 214,000
CO . . . 55,000	LA. . . 185,000	MO . . 300,000
FL. . . 240,000	LA. . . 129,000	MO . . 395,500
FL. . . 125,000	MA . . 120,000	NM . . 160,000
FL. . . 270,000	MA . . 355,000	NY . . 165,000
FL. . . 225,000	MA . . 150,000	NC . . 295,000
FL. . . . 90,000	MA . . 235,000	NC . . . 90,000
FL. . . . 90,000	MA . . 100,000	PA. . . . 95,000
FL. . . 275,000	MA . . . 85,000	VA . . . 94,000
GA . . 150,000	MA . . 115,000	VA. . . 150,000
GA . . 225,000	MA . . 120,000	

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(Continued from Page 405)

INTERNAL MEDICINE

May 22-26—**23rd Annual Advances in Internal Medicine**. UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 33 hrs. $645. Contact: UCSF.

July 20-22—**Therapeutic and Diagnostic Pancreatico-Biliary Endoscopy.** California Pacific Medical Center at Ana Hotel, San Francisco. Thurs-Sat. 22.5 hrs. $750. Contact: Laura Johnson, 2351 Clay St, Rm 373, San Francisco 94115. (415) 923-3242.

ONCOLOGY

June 4—**Lymphoproliferative Disorders.** California Tumor Tissue Registry at Westin South Coast Plaza, Costa Mesa. Sun. 8 hrs. Contact: Anne Chism, CTTR, 11021 Campus Ave, AH 335, Loma Linda 92350. (909) 824-4788.

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

June 1-2—**Annual Ophthalmology Symposium**. UCD at Vizcaya, Sacramento. Thurs-Fri. Contact: UCD.

June 2—**Annual UCD Ophthalmology Symposium.** UCD at Vizcaya Pavilion, Sacramento. Fri. 6 hrs. $95. Contact: UCD.

OTOLARYNGOLOGY

June 4-9, September 10-15—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach**. UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

November 2-4—**San Francisco Otology-Neurotology—1995.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 24 hrs. Contact: UCSF.

PATHOLOGY

May 25-27—**Current Issues in Anatomic Pathology: 1995**. UCSF at Mark Hopkins Intercontinental Hotel, San Francisco. Thurs-Sat. 19.5 hrs. $195-$495. Contact: UCSF

August 12-19—**16th Annual Comprehensive Fine Needle Biopsy Course**. UCSF at Ritz-Carlton, San Francisco. 1 wk. 27 hrs. $950. Contact: UCSF.

PEDIATRICS

June 23-25—**Current Concepts in Pediatric Respiratory Diseases.** Children's Hospital San Diego and UCSD at San Princess Resort. Fri-Sat. 16 hrs. Contact: Children's Hospital, 3020 Children's Way-5021, San Diego 92123. (619) 576-4072.

July 21-22—**3rd Annual Pediatrics Update**. Stanford University at Lucile Packard Children's Hospital. Fri-Sat. Contact: Elinor Meyer, Continuing Medical Education, 725 Welch Road, Palo Alto 94304. (415) 497-8554.

PSYCHIATRY AND NEUROLOGY

May 24-26—**14th Annual Child Abuse and Neglect Conference**. UCD at Red Lion Hotel, Sacramento. Wed-Fri. 15 hrs. Contact: UCD.

July 25-29—**Neuropsychiatric Emergencies-Crisis.** American Academy of Family Physicians with Southern California Neuropsychiatric Institute at Hapuna Prince Beach Hotel, Kamuela, Hawaii. Tues-Sat. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

RADIOLOGY

July 16-20—**Advanced Imaging of the Spine**. UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 24 hrs. $550. Contact: UCSD.

October 21-22—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. 13 hrs. $375. Contact: UCSD.

October 23-27—**20th Annual San Diego Postgraduate Radiology Course**. UCSD at Hotel del Coronado. Mon-Fri. 27 hrs. $575. Contact: UCSD.

October 27-28—**15th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado. Fri-Sat. 14 hrs. $375. Contact: UCSD.

SURGERY

June 14-17—**12th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency, La Jolla. Wed-Sat. Contact: Rebecca Quiring, 3905 Waring Road, Oceanside 92056. (619) 940-2066.

July 3-6—**Aesthetic Plastic Surgery of the Face, Eyes, Nose and Neck.** International Surgical Society at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. 19 hrs. $700. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

GENERAL/MULTIDISCIPLINARY

June 2-4—**8th Annual Medical Office Laboratory.** San Diego State University at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $475. Contact: Nanacy Geiser, College of Extended Studies. (619) 594-6255.

June 19-23—**Medical Informatics Introductory Short Course.** Stanford University's Center for Advanced Medical Informatics at Stanford. Mon-Fri. 34.25 hrs. $900-$1300. Contact: Irene Zagazeta, (415) 723-6979.

June 23—**The Future of American Medicine: A Bioethics Symposium**. UCD at Cancer Center Auditorium. Fri. 3 hrs. Contact: UCD.

August 28-September 1—**Medical Informatics Introductory Short Course**. Stanford University's Center for Advanced Medical Informatics at Stanford. Mon-Fri. 34.25 hrs. $900-$1300. Contact: Irene Zagazeta, (415) 723-6979.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs. (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 408)

Armed Forces Institute of Pathology
American Registry of Pathology

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This conference will explore recent advances in controversial areas of surgical pathology. Drawing on the 45,000 to 50,000 difficult, unusual, or "classical" cases seen each year at the AFIP, the presentations will detail the latest approaches available to aid in the diagnoses of these cases. Areas to be covered, among others, include hepatic, gastrointestinal, pleural, pulmonary, bladder, prostate, breast, ovarian, uterine, and bone pathology along with discussion of the surgical pathology of HIV infection and AIDS.

The Armed Forces Institute of Pathology designates this continuing medical education activity for approximately 24.75 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association and Category 2A by the American Osteopathic Association, If all sessions are attended.

Information Contact:

AFIP Education Dept.
14th & Alaska Ave., NW
Washington, DC, 20306-6000, USA
Tel: (301) 427-5231
Fax: (301) 427-5001
Toll: (800) 577-3749 (U.S. only)
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  Major Spry, World Headquarters of Jehovah's Witnesses, Brooklyn, NY
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- **Oxygenated Blood Substitutes, Plasma Expanders, Erythropoietein and Other Growth Factors**
  H. Franklin Bunn, M.D., Harvard Medical School, Boston, MA

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  Christopher M. Duma, M.D.
- **A Unified Treatment Approach Without Blood Transfusions in Cardiac Patients** *Stanley H. Wishner, M.D., Ray V. Matthews, M.D., Manuel R. Estioko, M.D., David S. Cannom, M.D., Gregory L. Kay, M.D.*
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- **International Impact - Future Dynamics of Bloodless Medicine & Surgery**
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FOR MORE INFORMATION:
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(Continued from Page 406)

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 24-28—**Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center, Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 28-August 1—**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Medical Education, Primary Children's Medical Center, Salt Lake City, at Sun Valley Resort, Sun Valley. Fri-Sun. Contact: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City, UT 84113. (801) 588-2000.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Fri-Sat.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

May 26-28—**20th Annual Conference on Neonatal/Perinatal Medicine.** The Center for Pediatric Continuing Education at the Cliff Lodge at Snowbird. Fri-Sun. Contact: PCMC.

June 7-10—**1995 Summer Pediatric Neurosurgery Symposium**. University of Utah School of Medicine at Stein Eriksen Lodge in Deer Valley, Park City. Wed-Sat. Contact: UUSM.

June 19-21—**17th Annual Conference on Common Problems in Pediatrics.** The Center for Pediatric Continuing Education at the University Park Hotel, Salt Lake City. Mon.-Wed. Contact: PCMC.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Education at Sun Valley Resort, Sun Valley, Idaho. Fri-Sun. Contact: PCMC.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

(Continued on Page 410)

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Sponsored by the University of California School of Medicine at San Francisco Office of Continuing Medical Education. CME Credits vary per course.

Topic	Date	Location
Advances in Internal Medicine	May 22-26	Ritz-Carlton, San Francisco
Advances in Internal Medicine	June 19-23	UCSF Campus, San Francisco
Critical Care Cardiology	August 10-12	Ritz-Carlton, San Francisco
Essentials of Primary Care	August 20-25	Squaw Valley, California
Clinical Care of the AIDS Patient	August 24-29	Sun Valley, Idaho
Design and Methods of Clinical Trials	September 14-15	Sir Francis Drake, San Francisco
Gastroenterology	September 29-October 1	ANA Hotel, San Francisco
Cardiology Update	October 5-7	Carmel Valley Resort, California
Primary Care Medicine: Principles and Practice	October 11-13	Ritz-Carlton, San Francisco
Recent Advances in Pulmonary and Critical Care Medicine	October 19-21	ANA Hotel, San Francisco
Occupational and Environmental Medicine	October 23-27	Miyako Hotel, San Francisco
Electrocardiography and Arrhythmias	October 28	ANA Hotel, San Francisco

(Continued from Page 408)

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 20-21—**PALS**. Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

May 26-27—**Laparoscopy: Surgery of the Colon and Appendix**. Seattle. Fri-Sat. Contact: U/W.

June 1-3—**Primary Care Update of OB-GYNs.** Seattle. Thurs-Sat. Contact: U/W.

June 2-3—**6th Update on Travel and International Medicine**. Seattle. Fri-Sat. Contact: U/W.

June 3-4—**PALS**. Seattle. Sat-Sun. Contact: Children's Hospital Medical Center, (206) 526-1050.

June 7-10—**Bariatric Medicine**. Seattle. Wed-Sat. Contact: U/W.

June 11-14—**Genomic Information: Ethical Implications.** Seattle. Sun-Wed. Contact: U/W.

July 20-23—**Comprehensive Review in Toxicology.** Tacoma. Thurs-Sun. Contact: Madigan Army Medical Center, (206) 968-0118.

July 31-August 5—**Summer Seminar in Health Care Ethics**. Seattle. Mon-Sat. Contact: U/W.

August 4-5—**Otolaryngology Update**. Tacoma. Fri-Sat. Contact: Madigan Army Medical Center, (206) 968-0118.

August 17-18—**CME Networking in the Northwest**. Port Ludlow. Contact: Valley Medical Center, (206) 575-4721.

August 22-25—**Trauma Radiology: 1995**. Seattle. Tues-Fri. Contact: IMM, (713) 965-0566.

September 9-13—**Intensive Training Workshop in Dialectical Behavior Therapy**. Seattle. Sat-Wed. Contact: U/W, (206) 543-9886.

September 11-15—**23rd Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 14-16—**Symposium on Teaching Internal Medicine**. Seattle. Thurs-Sat. Contact: U/W.

September 22-23—**Laparoscopic Surgery: Upper GI**. Seattle. Fri-Sat. Contact: U/W.

September 28—**Infectious Disease Conference.** Renton. Thurs. Contact: Valley Medical Center, (206) 575-4721.

October 21-22—**ACLS**. Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

December 1-2—**Laparoscopic Surgery: Hernia**. Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

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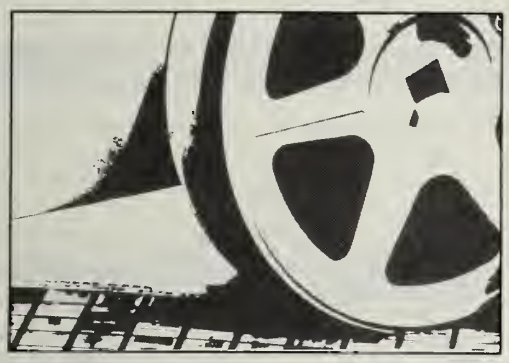

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Articles

Neurologic Complications of Lightning Injuries

MICHAEL CHERINGTON, MD; PHILIP R. YARNELL, MD;
and SCOTT F. LONDON, MD, *Denver, Colorado*

Over the past ten years, we have cared for 13 patients who suffered serious neurologic complications after being struck by lightning. The spectrum of neurologic lesions includes the entire neuraxis from the cerebral hemispheres to the peripheral nerves. We describe these various neurologic disorders with regard to the site of the lesion, severity of the deficit, and the outcome. Damage to the nervous system can be a serious problem for patients struck by lightning. Fatalities are associated with hypoxic encephalopathy in patients who suffered cardiac arrests. Patients with spinal cord lesions are likely to have permanent sequelae and paralysis. New technology for detecting lightning with wideband magnetic direction finders is useful in establishing lightning-flash densities in each state. Florida and the Gulf Coast states have the highest densities. Colorado and the Rocky Mountain states have the next highest.

(Cherington M, Yarnell PR, London SF: Neurologic complications of lightning injuries. West J Med 1995; 162:413-417)

Most serious lightning injuries occur when there is damage to either the cardiovascular or neurologic systems. The nervous system is particularly susceptible to damage from lightning strikes. Despite this vulnerability, a single large series describing the neurologic complications of lightning injuries has not been reported. Because of the sporadic nature of lightning, the literature consists of articles reporting only a few, usually one or two, cases.[1-31] Over the past ten years we have examined and treated 13 patients with neurologic complications following lightning injuries and believe this is the largest single series of such sequelae.

These patients represent a wide spectrum of neurologic problems. Two new cases are reported here. The remaining 11 have been reported previously,[32-34] but these cases will be summarized here to delineate the spectrum of neurologic sequelae from lightning injuries.

Report of Cases

Case 1

The patient, a 57-year-old-man, was struck by lightning while sitting in his golf cart. At the site, he was found to be unconscious and in ventricular fibrillation. After treatment with DC shock and the intravenous administration of lidocaine, epinephrine, and atropine sulfate, his rhythm converted to sinus tachycardia with a rate of 140 beats per minute. He was transported to the hospital, but never regained consciousness. His left tympanic membrane was ruptured. His pupils reacted minimally to light stimulation. He had no volitional movements of his limbs, but did have occasional myoclonic activity in all four limbs. He was diagnosed as having severe hypoxic brain injury due to cardiac arrest and treated with divalproex sodium. A computed tomographic (CT) scan of the brain showed findings consistent with hypoxic encephalopathy (Figure 1). The patient died three days after admission.

Case 2

The patient, a 30-year-old man, walked to his closed glass patio door during an evening lightning storm. The right side of his face was near the glass door. He had an atypical sensation in his right eyebrow that felt like "static electricity" or "crawling ants." A moment later he saw a flash of lightning on his patio. On awakening the next morning, he noticed that he had weakness of the right side of the face, and he could not close his right eye during his morning shower. A neurologic examination four days later revealed an isolated right facial nerve palsy. He did not have any hearing loss, hyperacusis, or abnormalities of taste. Tympanic membranes and gross testing of hearing were normal. Magnetic resonance imaging (MRI) of the brain was normal. At follow-up clinical examination three weeks later, the patient was improved with only mild residual facial weakness. An electromyogram showed abnormalities consistent with an acute neurogenic lesion. Fibrillation potentials were found in muscles supplied by the right facial nerve. He did not return for electrophysiologic evaluation of seventh cranial nerve function.

Discussion

Our 13 patients who suffered neurologic complications after being struck by lightning are listed in Table 1.

From the Lightning Data Center, St Anthony Hospital Central, Denver, Colorado.
Reprint requests to Michael Cherington, MD, Lightning Data Center, St Anthony Hospital, 4231 W 16th Ave, Denver, CO 80204-1374.

ABBREVIATIONS USED IN TEXT

CT = computed tomographic
MRI = magnetic resonance imaging

Cases of neurologic sequelae to lightning strikes described in clinical or neuropathologic detail in the English-language literature are listed in Table 2.[1-31] In addition, neurologic complications were summarized from cases in the European literature (mostly from Germany and France), including the following: Parkinson's disease, 3 cases; cerebellar ataxia, 1 case; spinal amyotrophy, 9 cases; stroke—aphasia, hemiparesis—7 cases.[35]

We excluded from our literature review those patients who had no serious neurologic sequelae, but who may have had one of the following symptoms: transient loss of consciousness, transient amnesia, transient paresis or paresthesias, cataracts or other ophthalmic problems, hearing loss and other eighth nerve problems, or psychological problems. According to some estimates, nearly 75% of all lightning victims suffer a brief period of loss of consciousness, and 80% suffer brief periods of paresthesias or pareses.[7,36,37] Psychological features of lightning strikes have been described elsewhere.[18,38]

With our 13 cases and the cases in the literature in mind, we have addressed the following questions:

- Why do so many cases occur in Colorado?
- Who is likely to suffer a lightning injury with neurologic complications?

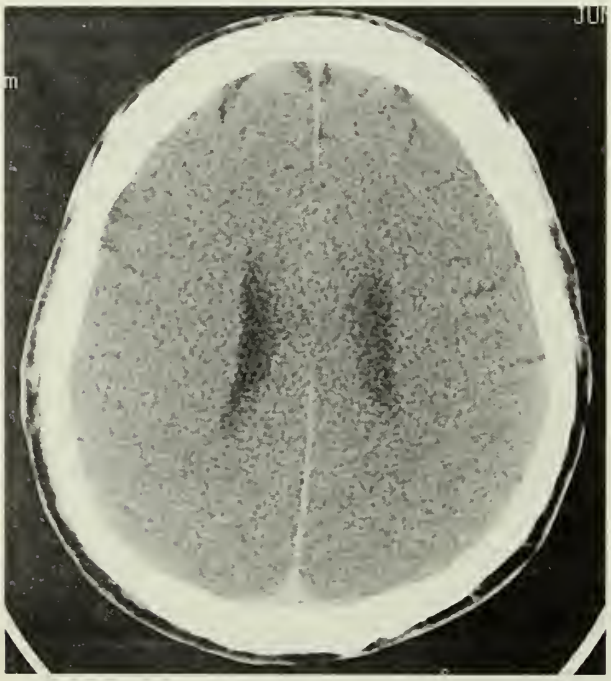

Figure 1.—The brain computed tomographic scan shows loss of gray-white differentiation and absence of sulci, consistent with hypoxic brain injury.

- What is the spectrum of neurologic damage?
- What are the most serious neurologic complications?

Why Do So Many Cases Occur in Colorado?

Colorado has a high lightning-flash density. With the development and use of the wideband magnetic direction finders, the number of cloud-to-ground lightning flashes per unit of time per unit area can be measured.[39] The North American continent is covered by a network of magnetic direction finders that allow for the determination of lightning-to-ground flash density for each state.[40] Florida and the other Gulf Coast states have the highest densities, and Colorado and the Rocky Mountain states have the next highest.[41] The number of lightning injuries and deaths is highest in those states with high lightning-flash density. Furthermore, a recent analysis of numbers of lightning injuries and deaths from several data sources in Colorado elicited even more cases than listed in the National Oceanic and Atmospheric Association's *Storm Data*.[42]

Who Is Likely to Suffer a Lightning Strike With Neurologic Complications?

Our experience closely parallels that in the medical literature with regard to sex and age of lightning victims.Most are men. Only 2 of our 13 patients were women; 7 of the 37 patients in the literature were women. The average age of our 13 patients was 27.2 years with a range of 11 to 64 years. The average age of the patients in the literature was 27.2 years with an age range of 7 to 70 years.

Of our 13 patients, 9 were engaged in outdoor recreational activity when they were struck by lightning. These activities are representative of those listed in the literature.[32,43] Outdoor lightning victims are most often found in two categories: occupational and recreational. Farming, roofing, and ranching are among the more dangerous occupations. High on the list of recreational activities associated with lightning injuries and deaths are golfing, fishing, swimming, boating, camping, hiking, and field sports.

Lightning strikes occur in one of three ways:

- *Direct strike*. This is the most serious type of lightning strike and is usually fatal.
- *Side flash*. This is a much more common form. In this type, lightning first strikes another object, such as a tall tree, and then the current takes the path of least resistance by "flashing" to the person who is standing next to the tree.
- *"Stride potential."* After lightning strikes the ground, electrical current travels along the surface of the earth. If a person happens to be standing in the path of the current with the legs astride, there is likely to be a voltage difference between each foot. The current may then take a path up one leg and down the other. In the case of a rock climber, the current may enter the body

TABLE 1.—*Neurologic Complications of Lightning Strikes*

Case	Age, yr	Sex	Complication	Site	Outcome
1	38	M	Hypoxic encephalopathy	Ski slope	Died
2	11	M	Hypoxic encephalopathy	Football field	Died
3	57	M	Hypoxic encephalopathy	Golf course	Died
4	20	M	Hypoxic encephalopathy	Roof	Impaired
5	33	M	Cerebellar lesion	Tent	Improved
6	64	F	Cerebellar dysfunction	Horse trail	Improved
7	15	M	Cerebellar infarction	Campsite	Improved
8	27	F	Concussion	Metal fence	Prolonged poststress
9	10	M	Concussion; incoordination	Campsite	Improved
10	57	M	Spinal cord lesion	Under tree	Paralyzed
11	16	M	Spinal cord lesion	Campsite	Paralyzed
12	21	M	Spinal cord lesion	Work site	Paralyzed
13	31	M	Cranial nerve VII injury	Near window	Improved

through an arm touching a boulder and exit through the lower extremities.

In addition to sustaining damage from the primary effects of lightning, patients are vulnerable to secondary injuries from direct physical trauma. Physical trauma should be considered in patients who suffer secondary fractures of the head and cervical trauma from falling if they are rendered unconscious. Patients may also be injured from falling debris such as broken tree trunks. Clinicians should also be aware of blast injuries resulting from the explosive forces associated with thunder. Ruptured tympanic membranes are the most common blast injuries found in lightning victims.

Although cardiac and neurologic damage is responsible for most of the morbidity and mortality of lightning victims, other organ systems are also vulnerable. Clinicians must be aware of other complications including rhabdomyolysis, renal failure, adult respiratory distress syndrome, pulmonary edema, cataracts, uveitis, and retinal lesions.[30,44,45]

Many of the abnormalities seen in lightning victims resemble those that occur in patients who suffer electric shock from generated high-voltage-electricity accidents. There are some differences, however. Those injured from electrical accidents are more likely to have severe burns, rhabdomyolysis, muscle necrosis, deep tissue damage, and gangrene. As a result, they are more likely to suffer renal failure and to need surgical amputation of limbs.

The reason for these more severe burns and tissue necrosis in electrical accidents relates to the longer duration of exposure to alternating current compared with the brief exposure to the direct current of lightning. Alternating current at 60 Hz tends to cause tetanic muscle spasms. When this happens, patients may be unable to release their grip from the power source, and therefore the duration of contact is increased. The ultimate degree of injury in either lightning or technical electrical trauma is related to the amount of current, the time of passage, the path of the current, and the resistance of the specific tissue.[11,32,46]

What Is the Spectrum of Neurologic Damage?

The cases already described in the literature involved lesions of the entire neuraxis. Our experience is consistent with those reports. We have treated patients with

TABLE 2.—*Literature Review of Lightning Neurologic Sequelae*

Case	Age, yr	Sex	Neurologic Sequelae	Reference
1	--*	M	Seizures	Critchley, 1934[1]
2	38	F	Wilson's disease	Young, 1934-1935[2]
3	52	M	Parkinson's disease	Langworthy, 1936[3]
4	38	F	Hemiparesis	Draper, 1937[4]
5	39	M	Extrapyramidal syndrome	Paterson and Turner, 1944[5]
6	28	M	Small cerebral hemorrhages	Lynch and Shorthouse, 1949[6]
7	18	M	Small cerebral hemorrhages	Lynch and Shorthouse, 1949[6]
8	51	M	Intracranial hemorrhage	Arden et al, 1956[7]
9	52	M	Epidural hematoma	Morgan et al, 1958[8]
10	10	M	Seizures	Ravitch et al, 1961[9]
11	15	M	Anoxic encephalopathy	Hanson and McIlwraith, 1973[10]
12	68	M	Parkinson's disease	Apfelberg et al, 1974[11]
13	15	M	Cerebral edema	Kravitz et al, 1977[12]
14	14	F	Cerebral edema	Myers et al, 1977[13]
15	7	F	Cerebral hypoxia	Myers et al, 1977[13]
16	15	F	Spinal atrophy	Myers et al, 1977[13]
17	21	M	Subarachnoid hemorrhage	Strasser et al, 1977[14]
18	25	M	Myelopathy	Sharma and Smith, 1978[15]
19	26	M	Cerebellar syndrome	Suri and Vijayan, 1978[16]
20	10	M	Seizures	McCrady-Kahn and Kahn, 1981[17]
21	11	M	Cerebellar ataxia	Kotagal et al, 1982[18]
22	9	M	Cerebral edema	Kotagal et al, 1982[18]
23	29	M	Cerebral infarct	Krob and Cram, 1983[19]
24	46	M	Truncal ataxia	Krob and Cram, 1983[19]
25	34	M	Cerebral edema	Krob and Cram, 1983[19]
26	20	M	Intracranial hemorrhage	Mann et al, 1983[20]
27	21	M	Hemiparesis	Peters, 1983[21]
28	31	F	Median nerve lesion	Amy et al, 1985[22]
29	22	M	Basal ganglia hematoma	Stanley and Suss, 1985[23]
30	15	M	Parietal infarct	Frayne and Gilligan, 1987[24]
31	22	M	Progressive myelopathy	Davidson and Deck, 1988[25]
32	58	M	Cerebellar syndrome	Morocutti et al, 1989[26]
33	70	F	Bulbar palsy	Saddler and Thomas, 1990[27]
34	45	M	Sagittal sinus occlusion	Lehman, 1991[28]
35	36	M	Autonomic failure	Weeramanthri et al, 1991[29]
36	19	M	Polyneuropathy	Hawkes and Thorpe, 1992[30]
37	15	M	Intracranial hematoma	Steinbaum et al, 1994[31]

*Age not given.

lesions involving the neocortex, cerebellum, spinal cord, and peripheral nerve.

The neuropathy of lightning injuries was described 60 years ago.[1] The neuropathologic findings of the central nervous system include the following: focal petechial hemorrhages and chromatolysis of pyramidal cells, Purkinje's cells of the cerebellum, and anterior horn cells. The most striking pathologic abnormality of peripheral nerves is a localized ballooning of myelin sheaths. The introduction of imaging techniques (MRI and CT scans) has given clinicians an ability to learn about the site and characteristics of these lesions that previously could be learned only at postmortem examinations.

Both our experience and that reported in the literature are similar in showing that central nervous system lesions are much more common than peripheral nerve lesions. Lesions of the brain are the most common neurologic complications. These lesions include the following processes: cerebral infarction, hypoxic encephalopathy often due to cardiac arrest, basal ganglial degeneration, and intracranial hematoma. Myelopathies and cerebellar lesions occur less often. Peripheral nerve lesions are most uncommon in our experience and are rarely reported in the literature. We saw only one patient with a cranial nerve lesion. He had an isolated facial nerve lesion, which is rare following a lightning strike. The largest number of cases of spinal amyotrophy are detailed in the European literature.[35]

Brief sympathetic nervous system instability characterized by pulseless, cyanotic, and weak extremities is common in victims of lightning strikes. These signs, along with tachycardia and hypertension, resolve in a matter of minutes or hours and are the result of increased catecholamine release.[12] The term "keraunoparalysis" has been used for the short-lived limb weakness associated with this hyperadrenergic state.[30] Permanent dysfunction of the sympathetic nervous system as the result of lightning injuries is much less common.[29,30]

Delayed neurologic syndromes have been described rarely after both lightning and electrical trauma.[1,35] These delayed syndromes (myelopathy and spinal muscular atrophy) are reported to occur days, weeks, and even months after the electrical trauma. The mechanism is unknown. In an article on the delayed syndromes in patients with electrical injuries, it was speculated that exposure to electric fields is similar to the effects of irradiation.[47] That there is a cause and effect between electrical trauma and a delayed pathologic response in lightning strike victims has yet to be proved. With regard to the possibility that delayed and progressive syndromes can be caused by lightning and electrical trauma, the following caution has been offered[48(p236)]:

> The attempt to link together a series of alleged facts or assumptions, each improbable in a particular degree, as the basis for a conclusion, contrary to the cumulative mathematical chances, may lead to serious error, whether or not it is honestly or sincerely arrived at.

What Are the Most Serious Neurologic Complications?

Three of our patients died; all had severe hypoxic encephalopathy after suffering cardiac arrest. Two were struck at high elevations in the Rocky Mountains. One was skiing in April; the other was struck in June while sitting in a golf cart. The third was a child who was struck while playing football. The cerebral edema evident by imaging studies in our patients is a posthypoxic, cytotoxic edema due to cardiac arrest.[49]

The surviving ten patients can be divided into three groups based on the level of their neurologic lesions:

- *Lesions above the foramen magnum.* All of these patients suffered an initial major insult. All of them eventually recovered, however. The lesions included cerebral infarction and cerebellar atrophy. The patient with cerebellar atrophy is of particular interest because the MRI uncovered atrophy of the cerebellar vermis within days after the lightning strike. This first case of a cerebellar syndrome after lightning strike, verified by MRI, provided evidence of possible rapid degeneration of the cerebellum.
- *Cranial nerve palsy.* One patient had an ipsilateral seventh nerve palsy, which subsequently abated.
- *Spinal cord lesions.* These patients were all left with a major deficit such as paralysis and did not return to their normal preinjury state.

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Articles

Immunopathologic Effects of Silicone Breast Implants

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Silicone-gel breast implants have been associated with a myriad of autoimmune and connective tissue disorders by anecdotal reports and small observational series. To date, no prospective epidemiologic studies have been done to substantiate these observations, but an increasing body of literature is being developed and older studies are being recognized that point to immunotoxic or inflammatory effects of these breast implant components. The development of disease due to implants would depend on the interaction of genetic host factors so that only a few patients would potentially be at risk. Based on the example of other chemically mediated disorders, such as scleroderma in association with silica exposure, latency periods of more than 30 years before disease develops may be possible. Herein we review studies on silicone and immunity.

(Teuber SS, Yoshida SH, Gershwin ME: Immunopathologic effects of silicone breast implants. West J Med 1995; 162:418-425)

Silicone-gel implants for breast augmentation and reconstruction have been in use since 1962.[1] Local complications have long been known to occur, primarily consisting of capsular contracture,[2-5] which is a hardening of the implant to palpation due to contracture of the fibrous capsule that normally forms (to varying degrees of thickness) around the implanted foreign body.[2-7] In two series, noticeable capsular contracture developed in as much as 40% to 50% of patients.[3,4] Ruptures can occur either intracapsularly or with extracapsular extension and spread of the gel to the chest wall or axilla. The exact incidence is not known. Virtually all implants have been shown to "bleed" silicone into the local microenvironment,[6] which can be reflected in histologic findings of foreign-body granulomas in the capsular tissues or regional lymph nodes.[7-9] More recent observations using magnetic resonance spectroscopy have demonstrated silicon compounds in the blood of some women with silicone breast implants, as well as evidence of silicone migrating to the liver.[10]

The controversy over the safety of silicone-gel implants has focused not on local complications but rather on the postulated link between the implanted gel and systemic illnesses or symptoms. Well-publicized anecdotal reports have raised concerns, especially in regard to scleroderma, but no prospective clinical series that clearly supports a link between connective tissue disease and implants as yet exists. Because of the lack of studies actually proving the safety of implants, the United States Food and Drug Administration, in its 1992 review of medical devices, decided that the implants should be removed from the market except for use in surgical reconstruction as part of clinical trials.[11] This has spurred research on the bioreactivity of silicone and of clinical observations of patients with implants. Herein we review the chemical properties of silicone implants and bench research studies pointing to adverse immune effects.

Chemistry of Silicone

Silicon constitutes about 28% of the earth's crust by weight.[12] It is an important trace mineral in bone formation and mineralization.[12] Silicon is also associated with glycosaminoglycans, unbranched polysaccharide chains that covalently attach to core proteins to form proteoglycans, which are components of the connective tissue matrix.[13] Silicones are a family of synthetic polymers using silicon-oxygen chains with organic side groups. The silicones used in a multitude of medical products are heterogeneous with respect to polymer lengths, side-chain substitutions, and fillers used. Thus, great variation exists in the biologic and physical properties of these chemicals.

Many persons have had exposure to silicones in some form such as in simethicone (an antifoaming agent in antacids) or possibly in microscopic amounts in injec-

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
BSA = bovine serum albumin
CFA = complete Freund's adjuvant
Ig = immunoglobulin
PDMS = polydimethylsiloxane

tions where silicone oil is used to lubricate the syringe (such as for insulin), but it must be emphasized that the chemical properties of each product are unique. Figure 1 illustrates the synthetic process.[14,15] First, elemental silicon is produced by heating silica (SiO_2) with carbon. Silicon is then reacted with methyl chloride (CH_3Cl), followed by hydrolysis, which results in the formation of linear or cyclic low-molecular-weight siloxanes. Silanoate catalysts are added that break open the most prevalent siloxane, octamethylcyclotetrasiloxane, to form high-molecular-weight polydimethylsiloxane (PDMS) linear polymers, the silicone used in silicone-gel implants. The gel material is formed by controlling chain lengths and cross-linking to produce a desired viscosity. Platinum and hydride-containing polymers may also be added to the gel.[16] Within the cross-linked PDMS polymer matrix, lower-chain-length PDMS (less viscous oil) is still present.

The outer silicone rubber envelope is a dispersion of silicone elastomer wherein fumed silica (amorphous or particulate, 10 to 15 μm) is compounded with the PDMS polymer to act as a filler or a strengthening agent.[14,15] Hexamethyldisilazane, divinyltetramethyldisilazane, and cyclic or short linear siloxanes are some of the materials that can be used to treat the silica to favorably alter its chemical interactions with the PDMS polymers.[15,16]

Exposure to Implant Components

Local Exposure

Implants were previously thought to be inert, and after an initial mild, nonspecific foreign-body reaction to "seal off" the implant from the rest of the body by a thin collagenous layer, there would be no further interaction such as biodegradation or adherence to tissues.[17] In studies of implants removed because of capsular contracture, it has been shown that the surface of an implant becomes coated with albumin, fibronectin, transferrin, and other proteins, as well as with fibroblasts and macrophages.[18] The affinity of fibronectin for the surface of an unused, sterile, smooth silicone envelope was also investigated in which pieces were incubated in normal human serum or saline solution, and, after washing, a high amount of fibronectin was shown to be adhering to the surface.[18] Fibronectin is an important component of the extracellular matrix allowing cellular adherence and migration.

In 1978 Barker and colleagues conclusively showed that silicone-gel implants do "bleed" silicone gel through the implant shell.[6] Filter papers on which various brands and types of implants had been sitting for a week were sent to Dow Corning (Midland, Michigan) scientists for analysis. They reported that the "distribution, by molecular weight, of the leaked material corresponded to relative quantities of each gel species present inside the envelopes and was not shifted to the lower molecular weights."[6(p836)] This finding is of possible relevance because many of the initial studies in animals showing minimal tissue reaction to silicones used low-molecular-weight silicone oils, whereas later studies, to be discussed, showed more reactivity to the higher-molecular-weight gel species. Gel bleeding follows the principle that "like dissolves like"—that is, the gel and the envelope are manufactured from the same materials, and therefore the envelope is not impermeable to its contents. In a similar manner, hydrophobic human constituents such as triglycerides and other lipids can diffuse into prostheses.[19,20]

Numerous reports document the presence of periprosthetic silicone particles[21] shed from intact implant surfaces or, more commonly, amorphous refrac-

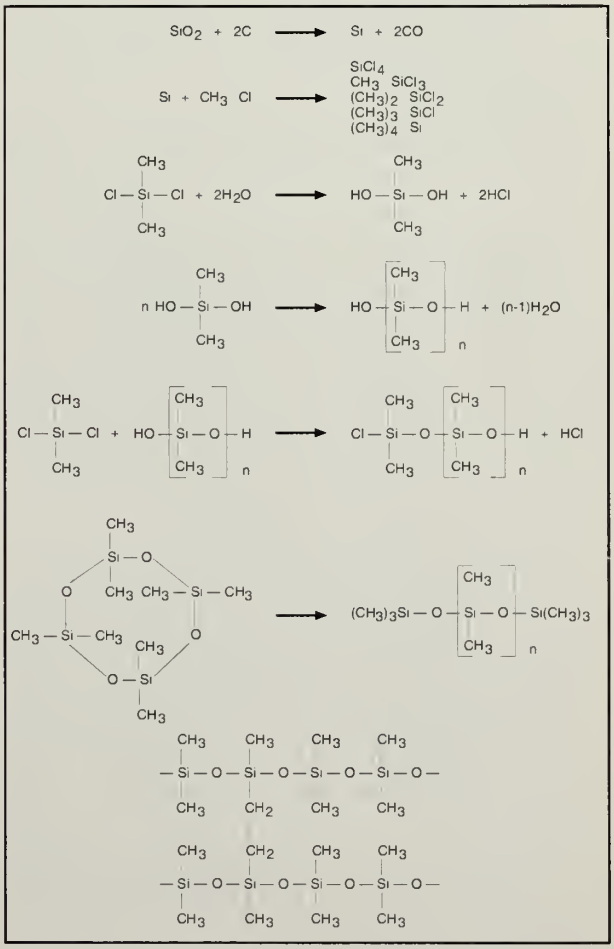

Figure 1.—The diagram shows an overview of polydimethylsiloxane (PDMS) synthesis. This includes, first, the production of elemental silicon (Si). Second, methyl chloride (CH_3Cl) treatment of silicone is used to produce methylchlorosilanes. Thereafter, prepolymers are formed and, ultimately, high-molecular-weight PDMS from cyclic prepolymers. "Curing" occurs using cross-linking agents such as peroxides.

tile material (either intracellular or extracellular) and foamy histiocytes with vacuoles—presumed to represent silicone oils that were removed by xylene used in histologic slide processing.[2,3,22,23] Studies have also documented the high content of silicon in these tissues, affirming that the materials seen are likely silicones.[23-26] Periimplant silicone has been found in both tissues with little or no visible inflammation and those capsule tissues with extreme fibrosis, mononuclear cell infiltrates, granulomas, and calcification.[26] It is hypothesized that the uptake of silicone by macrophages results in cellular activation and the secretion of inflammatory mediators,[27-30] resulting in chronic inflammation, the proliferation of fibroblasts, and collagen deposition around the implant. A recent study showed immunoreactivity in implant capsules for tumor growth factor β, insulin-like growth factors I and II, and some reactivity for platelet-derived growth factor β, nerve growth factor, and tumor necrosis factor-α. Mature skin scar tissue did not show any immunoreactivity for these growth factors.[31] It has also been proposed that low-grade bacterial contamination of the implant surface, rather than the body's reaction to silicone, may account for chronic inflammation in some cases.[32]

Silicone gel-filled implants account for the vast majority of implants that have been used. Saline implants pose the same exposure to the body of the components of the outer silicone rubber envelope. Polyurethane-coated gel-filled implants pose another exposure variable that will not be addressed in this review. These implants were removed from the market in 1991 when concern arose that the polyurethane foam can be degraded to constituents that include toluene 2,4-diisocyanate, a carcinogen in rats.[33] The polyurethane foam coating has been noted to separate from the implant and slowly degrade, provoking a foreign-body inflammatory response much like the response to silicone alone.[34]

Distant Exposure to Implant Components

Studies in animals done in the 1960s with small volumes of liquid silicone administered either subcutaneously or intraperitoneally in mice resulted in mild inflammation and fibrosis at the site of many of the subcutaneous injections and occasional collections of silicone-laden cells in the zona reticularis of the adrenal glands. Massive doses resulted in widespread visceral collections of vacuolated cells in lymph nodes, liver, kidneys, spleen, pancreas, adrenal glands, and ovaries.[35,36] Vacuoles, presumed to represent silicone fluid, were seen for several weeks in the peripheral blood neutrophils and some monocytes of mice and baboons after the subcutaneous or intraperitoneal administration of silicone fluid.[37]

It is evident also from human case reports that silicone droplets that bleed from an implant or shed elastomer particles from the outer implant shell do indeed undergo phagocytosis by macrophages and transport to distant organs. The most commonly reported involvement is of the axillary lymph nodes.[8,9] Silver and coworkers recently demonstrated silicon-containing material by electron-probe microanalysis in the skin, alveolar macrophages, and synovia of three patients with implants and connective tissue disorders.[38] Experience with migrated liquid silicone administered in humans—in which silicone has been found in alveolar macrophages associated with pneumonitis and in liver parenchyma with granulomatous changes—can be extrapolated to gel implants, but inadvertent intravenous or intra-arterial administration remains a possibility.[39,40] Shed silicone particles from dialysis tubing were reported to be the cause of granulomatous splenomegaly (with foreign-body reaction) in one patient suffering from splenomegaly-associated pancytopenia.[41]

Gel bleeding can explain the exposure of virtually all patients to at least microscopic quantities of silicone, but it should be kept in mind that implants do have a finite life span, and rupture, which may be contained by the capsular tissue or which may also involve the capsule, is probably inevitable. The actual incidence of implant rupture is not known.

Silicone could migrate away from the site of the breasts by several mechanisms: migration of silicone collections along fascial planes, probably influenced by gravity and muscle action[42]; uptake by macrophages that may enter lymphatic channels or the bloodstream[8,9]; release from dying macrophages with possible uptake by macrophages or other phagocytic cells, depending on site[37,43]; transfer from macrophage to lymphocyte by cytoplasmic bridging[44]; and the formation of emulsions with host molecules and subsequent dispersal.[45]

Biodegradation of Implant Materials

A point to keep in mind is that biodegradation products of silicone implants, or even chemical contaminants, may be more mobile and more important than an implant's original and primary constituents in any eventual manifestation of disease. Hydrolytic degradation may slowly affect lightly cross-linked polymers.[46] Silicones may be degraded by oxidants such as hydroxyl radicals that can cleave silicon carbide bonds. When exposed to water, silanol bonds could form that could result in new siloxane chain linkages. In addition, although silicones were reported to be resistant to acids and bases, under certain conditions, they may be susceptible to cleavage (C. W. Lenzt, "It's Safe to Use Silicone Products in the Environment," Dow Corning Chemical Corporation, Industrial Research Development, April 1980). A study on silicone bag-gel implants in dogs showed changes in mechanical properties after a year.[44] Anecdotally, in the operative report of one of our patients seen in the University of California, Davis, Rheumatology Clinic, the surgeon reported that the implant shell was no longer present at the time of explantation.

An internal Dow Corning report provides some of the first data on the biodegradation of organosilicones in humans. In 1980 a male volunteer inhaled about 20 mg of the DC-344 fluid; measurements suggested that near-

ly 20% of the estimated quantity of DC-344 fluid was excreted in the urine in the eight hours following exposure. The presence of monomethyl as well as dimethyl silicon in the urine implicated demethylation of the cyclic dimethyl species during human metabolism. Of greater concern is the presence of metabolites in the breast milk of a lactating woman who was exposed by inhalation (R. B. Annelin, "Trace Analysis of Organosilicon in Human Urine and Milk by the ASFT Technique," Dow Corning Toxicology Department File No. 3135-1, Series No. 1-0005-0752, 1980; and the Jefferson Group, Inc, "A Review of the Toxicological Information on Octamethylcyclotetrasiloxane and Related Government Action," Dow Corning Corp, 1992, pp 28402115-28402143).

The strongest data in the literature for biodegradation in vivo come from a series of articles detailing findings in a rat model by nuclear magnetic resonance spectroscopy.[10,47-50] These studies demonstrate the migration of silicones from both subcutaneous administration of a polysiloxane emulsion and from bag-gel implants to the lymph nodes and liver at 12 months. An interesting point is that there were shifts in the resonance peaks to those corresponding with hydrolyzed silicone and with silica. Neither of these resonances was present in the silicones before implantation, suggesting in vivo degradation.

Inflammatory and Immune Responses to Implants and Components

Local Tissue Response

In the most thorough investigation on tissue responses to various implant components,[16] rats were implanted subcutaneously with fumed silica, silicone gel, silicone fluid, silica-free implant shell, implant shell ("as manufactured"), xylene-extracted implant shell ("implant-ready"), and the evaporated xylene extract (possibly containing residual macrocyclics or platinum catalyst, but unknown). Rats were sampled at days 7, 14, 30, 60, and 90. All components showed inflammation to varying degrees, but the most intense inflammatory response was towards the fumed silica, with fibroblasts, lymphocytes, macrophages, plasma cells, and multinucleated giant cells. Cellular destruction was also evident with the fumed silica, reminiscent of what is seen with crystalline silica.[51,52] The silica-free shell was somewhat less reactive than the "implant-ready" extracted shell and showed less collagen capsule formation, which could possibly be attributed to mechanical factors (increased compliance). Although the authors of these studies do not propose that silica is released from implant shells, nuclear magnetic resonance studies done later make this a tenable hypothesis and may account for the differences seen.[47-50] The implant shell extract, which would not be expected to contain silica, had the greatest number of multinucleated giant cells. Amorphous silica has not been associated with pulmonary silicosis or scleroderma, unlike crystalline silica,[53,54] but it has not been as extensively studied.[55,56]

Tissue response to accidentally introduced siliceous material in the skin from concrete or rock can induce local silica granulomas that can mimic sarcoidosis. It has been proposed that many cases of sarcoid arising in scars are actually silica granulomas.[57,58] A series of 41 patients was recently published wherein the periprosthetic tissues were examined for magnesium silicate, which was hypothesized to be talc ($MgSi_4O_{10}[OH]_2$).[59] Of these 41 patients, 29 (71%) did have birefringent crystals in granulomas or in perivascular histiocytes. Silicone aggregates were not birefringent. Of the capsules, 70% showed free silicone, but 100% of the tissues did have empty cysts and vacuoles after xylene processing, suggesting dissolution of silicone before scanning electron microscopy. The presence of magnesium silicate and silicone was confirmed by scanning electron microscopy with energy-dispersive x-ray microanalysis. This is the first report of possible talc granulomas associated with breast implants. Talc is a known sclerosing agent[60] and is associated with granulomatous inflammation.[61,62] It also may have adjuvant properties in animal models.[60,63] The source of magnesium silicate in these patients is unknown; it may have been introduced on surgeons' gloves, on the implants, bled from the implant, or formed de novo as a degradation product. This is an area sure to receive more attention as further histologic studies are done.

Cellular Immune Response

In another internal Dow Corning report, the endotoxin-induced interferon type I production in mice was examined after pretreatment with various silicones. Dow Corning 360 fluid (DC-360, medical-grade silicone fluid used for administration in humans), mixed 1:1 with octamethylcyclotetrasiloxane (D4) in a volume of 0.3 ml administered intraperitoneally, substantially augmented the interferon production to endotoxin over that in the controls, and the production was twice as great as the response to D4 alone. The response lasted several days and was hypothesized to be due to transient effects on splenic macrophages (laden with oil droplets), with decreased endotoxin clearance (R. S. Lake and M. F. Radonovich, "Action of Polydimethylsiloxanes on the Reticuloendothelial System of Mice: Basic Cellular Interactions and Structure-Activity Relationships," Dow Corning Corporation Research Department Report No. 5409, 1975). This study reported a dramatic adjuvant action as well as local cellular response to various silicones.

Direct responses of lymphocytes to silicone were not demonstrable by lymphocyte transformation,[64] but delayed-type hypersensitivity to PDMS fluid incubated with syngeneic pooled guinea pig serum (presumed silicone-protein complexes formed) was shown in inbred guinea pigs inoculated intraperitoneally with the silicone-serum plus complete Freund's adjuvant (CFA) before intradermal challenge.[65] Challenges with saline solution, serum alone, and silicone alone did not produce notable responses. Histologic examination revealed

a moderate to pronounced lymphocytic infiltrate only at the silicone-serum site and a positive response to purified-protein derivative testing at the control site. The results suggest that silicone-protein complexes are immunogenic. The ability of silicone gel to act as an adjuvant in a delayed-type hypersensitivity system was examined recently by inoculating gel with bovine serum albumin (BSA), saline solution and BSA, or CFA and BSA. Subsequent BSA intradermal challenge showed that silicone gel produced a cellular response to BSA equivalent to that of CFA.[66]

Another recent study examined the polyclonal human T-cell activation that resulted from incubating T cells with inorganic silicate (not silicone). The results suggested that silicate may act as a superantigen. The suggestion was made that this may play a role in scleroderma associated with occupational silica dust exposure.[67]

Humoral Immune Response

Silicone gel and amorphous silica have been shown in studies of animals to have adjuvant effects on the humoral immune response, and the presence of silicone-gel implants in humans has been associated with a variety of autoantibodies and antisilicone antibodies. The earliest study on humoral adjuvancy of medical-grade PDMS was done by Dow Corning in an unpublished report in 1974 (W. F. Boley and R. R. LeVier, "Immunological Enhancing Activity of Organosilicon Compounds and Non-Functional Fluids," Dow Corning File No. 1063-19 [report reference 63]). An adjuvant is a substance that enhances the immune response to an antigen. Adjuvants have not been known to cause disease in humans; rather, they have been used to increase antibody responses to various antigens in immunizations. Some adjuvants, however, particularly CFA and pristane, can produce notable disease, including autoimmunity, in animals. Dow Corning compared the ability of various silicon-containing compounds to stimulate anti-BSA antibody responses in guinea pigs immunized with BSA-saline solution or BSA-organosilicone compounds; CFA was the standard positive control. DC-360, or medical-grade silicone fluid used for administration, caused a 5.0 $\log_2$ increase in titer, compared with 1.3 for saline solution and 8.1 for CFA. Not all the silicone fluids exhibited adjuvancy using this specific assay.

The ability of silicone gel from a mammary implant mixed in a 1:1 ratio with DC-360 fluid to enhance the antibody response to BSA in rats was tested in 1993.[68] DC-360 fluid alone enhanced the antibody response only slightly compared with saline solution, but the response to the gel-fluid mixture was as great as that to the CFA. Dow Corning, in another internal report, repeated this research and came to similar conclusions—the gel potentiated the immune response considerably, whereas the DC-360 fluid response was only marginally notable, if at all (P. C. Klykken, T. W. Galbraith, M. R. Woolhiser, et al: "A Humoral Adjuvancy Study of Dow Corning Silicone Fluids Alone [360 fluid, 20cs; 7-2317, 1000cs] and Dow Corning 360 Fluid, 20cs, Mixed With Dow Corning Mammary Gel [Q7-2159a] or McGhan Mammary Gel in the Rat," Dow Corning Corporation Report 1993-10000-37981, 1993). These findings appear to complement the histologic reports that the higher-molecular-weight silicone gel produces more inflammation than the fluids.[16]

Studies on the adjuvancy of crystalline and amorphous silica suggest that effects on macrophages, which are the target of cytotoxicity by crystalline silica,[51,52] are primarily responsible. Crystalline silica was able in one system to stimulate antibody production to a T cell-dependent antigen, but not a T cell-independent antigen.[69] Another study suggested that nonspecific stimulation and expansion of the reticuloendothelial system were responsible for adjuvancy to crystalline silica.[70] Amorphous silica treated with various antigens was able to substantially enhance antibody response to the antigens except for BSA.[71] Patients with silicosis have had high titers of anticollagen type I antibodies and elevated levels of immunoglobulins—perhaps reflecting nonspecific B- and T-cell activation due to silica, postulated, as noted earlier, to be a superantigen[67]—and other autoantibodies including antinuclear antibodies (ANAs) and rheumatoid factors. It is not known whether the anticollagen autoantibodies are pathogenic or merely reflect the adjuvancy action of silica on a self-protein found in high quantities in the lungs of patients with silicosis.[72]

In our own studies, we looked at the anticollagen antibodies in women with silicone-gel breast implants and found that 26% of patients were positive for antibodies (>3 standard deviations above the enzyme-linked immunosorbent assay mean optical density of normal controls) against either native or denatured type I collagen. Only 2% of normal women had such autoantibodies. We hypothesized that if silicone induces an autoimmune response, reactivity would be expected against components of the peri-implant milieu, such as type I collagen.[73] We also examined reactivity to type II collagen; 20% of patients had antibodies against either native or denatured type II collagen. Western immunoblotting has subsequently been done on an expanded series of patients with anticollagen antibodies, with the results showing that the epitopes involved are different from those seen in the autoimmune diseases systemic lupus erythematosus and rheumatoid arthritis. Thus, it does not appear that these patients are in a prodromal phase of either of these autoimmune diseases, which some have associated with silicone implants.[74] Antibody responses against connective tissue proteins were also examined in women with implants. Results suggest that some patients produce antibodies against matrix molecules that have been altered from native conformation due to interaction with silicone, thus rendering them possibly more immunogenic.[75]

It also appears that antibodies can develop specifically against the silicone polymer itself, not just against associated connective tissue proteins. Two patients with

inflammatory reactions to silicone ventriculoperitoneal shunts exhibited immunoglobulin (Ig) G binding to silicone tubing in vitro.[76] A large study in women with implants showed substantial levels of IgG by enzyme-linked immunosorbent assay compared with normal controls, especially those women with ruptured implants. Most control patients did have background antisilicone antibodies.[77]

A higher-than-expected incidence of antinuclear antibodies was recently reported in women with implants.[78] Women with implants who were asymptomatic had an 18% incidence of positivity for ANAs (titers of at least 1:256) compared with 0% in the controls. Of women with various symptoms, but without a defined autoimmune disease, 26% were also positive for ANAs. In a series of patients with silicone-gel implants, 11 with autoimmune diseases and 13 with complaints such as myalgias or fatigue, the patients with autoimmune diseases had positive ANA tests, as expected (except one) but, in addition, 7 of 13 of the others were positive for ANAs with several bands of unknown specificity on immunoblotting.[79] The importance of antibodies to silicone or connective tissue components as they relate to possible disease is unknown at this time, but it is an issue of concern.

Discussion

Although no prospective epidemiologic studies that prove a relationship between silicone-gel implants and systemic disease have been done, two retrospective studies were recently published that could not establish a link, but lacked sufficient power to be considered definitive.[80,81] One was done in Sydney, Australia, and looked specifically at scleroderma; 4 of 251 women with scleroderma had implants, and 5 of 289 controls had implants.[80] At 90% power, this study has a minimum detectable relative risk of 5.3, and yet, with a disease like scleroderma, even a relative risk of 2.0 would be considered of great importance and could have been missed (S. H. Swan, PhD, School of Public Health, University of California, Berkeley, written communication, fall, 1994). Another study looked at all major connective tissue diseases, including, for unclear reasons, ankylosing spondylitis, which affected 3 women in the control group.[81] The minimum detectable relative risk for scleroderma based on the incidence in this study was 19.2 (with 90% power) (S. H. Swan, PhD).

It is possible that we will never be able to prove that a particular connective tissue disease, such as scleroderma, is associated with implants because of its overall rarity. However, researchers cannot assume that the patients with scleroderma reported to date in the literature are the only scleroderma patients with implants. In our own experience, we have examined eight patients with progressive systemic sclerosis who have not been reported in the literature. It is therefore misleading to take the number reported to date and divide it into 1 to 2.2 million—the putative number of women in the United States and Canada who have had implants in the past 30 years—to obtain a prevalence rate.[82] In addition, the denominator may be highly inaccurate because it is based on the number of implants sold and not on the actual number of women with implants. For example, in a series of 70 patients with implants in our clinic, more than 200 actual breast implants have been placed—many women required two or more surgical procedures to correct problems of capsular contracture or rupture. Also, the latency period for a disease such as scleroderma could be as long as 30 years if parallels can be drawn with scleroderma due to occupational silica exposure. Interested readers are referred to two recent publications that review the clinical reports of connective tissue disorders in patients with implants.[82,83]

It can be seen by the studies reviewed here that silicones are neither biologically nor chemically inert and that there is clinical and theoretical reason for concern. Patients may be exposed to implant constituents through gel bleeding, rupture, and biodegradation. The clinical importance of the adjuvant properties of many of the implant components is unknown. Prospective epidemiologic work and further studies that correlate the bioreactivity of silicone and its degradation products with clinical findings are anticipated. In the meantime, we do not routinely recommend that asymptomatic women who currently have intact silicone gel-filled implants undergo explantation. If a woman has an autoimmune disease, removal may be prudent, but the risks of a surgical procedure in each case must be individually clarified and balanced against the uncertain benefits of explantations, which could include psychological effects, the alleviation of local complications, or possible amelioration of the autoimmune disease process.

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* * *

Launching

She watches him launch it.

Petey, with his skipper
cap, his new toy boat,
a longed-for gift, adjusts
the sails, angles the rudder
till they're just right

for a light breeze. *Cast off!*
When the boat wallows, tips,
sails drenched with silver
dragging it under,
he's running, her son,

to the other side, shouting,
I'll bring you in.
What she, a grown woman,
a mother, couldn't do,
somehow bring her in

or get over to where
her lilac-blue girl
floats in a limbo
like this pool, shallow,
in some lonely marsh

down-hill from heaven.
Lilac-blue. She saw her.
Surfacing from twilight
sleep to rage and great
confusion. Sister Paul

hissing, *You said*
abort, no heartbeat,
Sister Luke pleading, *Please,*
let's baptize it,
while she's thinking, *Breathe,*

breathe in deep
to the baby who flops
in the doctor's hand, who mews
in air when she's slapped,
whose ribs scarcely move,

ribs that luffed like sails
when light air lapses
and wave wash stills
and the outbound ship's
adrift.

J. C. Todd©
Philadelphia, Pennsylvania

Articles

Costs of Minimally Invasive Laser Surgery Compared With Transurethral Electrocautery Resection of the Prostate

JOHN N. KABALIN, MD, *and* EDMOND D. BUTLER, MD, *Stanford, California*

We reviewed hospital charges for patients undergoing uncomplicated endoscopic surgical resection for symptomatic bladder outlet obstruction due to benign prostatic hyperplasia over a 1-year period at a single institution. Of 115 patients, 67 underwent transurethral electrocautery resection of the prostate, and 48 underwent endoscopic neodymium:yttrium-aluminum-garnet laser ablation of the prostate under direct vision. Analysis showed a cost differential between these 2 surgical treatments in excess of $2,000, favoring laser prostatectomy ($P < .0001$) over transurethral electrocautery resection. The single greatest difference between the treatments was the ability to manage all patients receiving laser treatment as outpatients, whereas the mean and median hospital stay after transurethral electrocautery resection was 3.0 days. Taking additional cost variables into account and decreasing the cost of laser delivery systems would further increase this cost differential in favor of laser therapy. The diminished postoperative morbidity associated with laser treatment also promises lower total costs over the long term.

(Kabalin JN, Butler ED: Costs of minimally invasive laser surgery compared with transurethral electrocautery resection of the prostate. West J Med 1995; 162:426-429)

Transurethral resection of the prostate (TURP) represents a leading health care expense in the United States. It is the most common serious operative procedure done on men in this country and is second only to cataract surgery as the major operation most costly to Medicare.[1] About 400,000 prostatectomies are done each year in the United States, representing an overall expense exceeding $5 billion.[2] This surgical procedure alone constitutes more than a third of the major surgical procedures done by urologists, and the clinical activities associated with it are estimated to absorb nearly a quarter of a practicing urologist's time.[1] With improvements in anesthesia and perioperative care, the mortality for TURP has been reduced to 0.2% over the past three decades, but the procedure itself has changed little in its technical execution, and postoperative morbidity has remained unchanged over the same period at a level of at least 18%.[3]

In recent years, driven by the high cost of TURP—not only in dollars spent but also in physician effort and overall patient morbidity—urologists have sought less expensive and less morbid means of treating the symptoms of bladder outlet obstruction caused by benign prostatic hyperplasia. Among the newer surgical technologies, transurethral endoscopic ablation of the prostate using a neodymium:yttrium-aluminum-garnet (YAG) laser source has now been studied extensively and applied in a large number of patients with encouraging results.[4-23] This technology appears efficacious in relieving symptoms due to prostatic hyperplasia and has been shown to produce substantially less morbidity than the standard TURP, including but not limited to decreased intraoperative irrigation absorption, better hemostasis, and overall diminished physiologic stress to patients. This relative lack of morbidity has allowed us to move the surgical treatment of benign prostatic hyperplasia to an outpatient, ambulatory, or same-day surgery setting.[14,17] Laser ablation of the prostate has also been shown to decrease total operative time for urologists and patients.[9,10] We examined the effect of these factors on the overall cost of surgical therapy for prostatic hyperplasia.

Patients and Methods

We retrospectively analyzed hospital charges and medical records of patients undergoing transurethral endoscopic surgical treatment at Stanford (California) University Hospital for the relief of bladder outlet obstruction due to benign prostatic hyperplasia during the period from July 1, 1992, through June 30, 1993. Patients undergoing open prostatectomy were excluded from this analysis. Similarly, patients with estimated excess hyperplastic tissue of more than 100 grams treated with laser were excluded because they would nor-

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ABBREVIATIONS USED IN TEXT

SD = standard deviation
TURP = transurethral resection of the prostate
YAG = yttrium-aluminum-garnet

mally have been treated by open prostatectomy and would not be considered candidates for standard TURP. In addition, patients undergoing concurrent surgical procedures such as inguinal herniorrhaphy at the time of transurethral prostatectomy were excluded from analysis because this affected the total operative time and hospital costs. For the purposes of this study, all TURP procedures were done by four experienced—range, 6 to 25 years in active surgical practice—private urologic practitioners (community urology service) without resident assistance. All laser procedures were performed by a single member (J.N.K.) of the Stanford academic urology faculty (university urology service), both with and without resident assistance.

A total of 115 patients were evaluable for the study period. Of these, 67 underwent standard TURP, and 48 were treated with laser prostatectomy. The mean patient age for TURP was 69.5 years (range, 45 to 89 years) and for laser prostatectomy was 70.0 years (range, 50 to 85 years). The mean estimated excess hyperplastic tissue in patients undergoing laser prostatectomy was 33 grams (range, 5 to 100 grams; standard deviation [SD] ± 21 grams). This compares with a mean resected tissue weight of 24 grams (range, 3 to 90 grams; SD ± 21 grams) in patients undergoing standard TURP. All laser procedures were performed with the Urolase (C. R. Bard, Inc) right-angle laser delivery fiber and a standard neodymium: YAG laser source. The operative technique used for laser prostatectomy has been described previously.[24]

Results

The mean total hospital charge to patients undergoing TURP at Stanford University Hospital during the period of this study was $8,262.06, exclusive of surgeons' and anesthesiologists' fees. No significant difference was found in hospital charges incurred between patients treated with TURP by any of the four urologic practitioners, as shown in Tables 1 and 2. By comparison, the mean total hospital cost for laser prostatectomy was $6,174.44, an average difference of $2,087.62 per patient (Student's *t* test, $P < .0001$).

TABLE 1.—*Mean Total Hospital Costs Incurred by Patients Treated With Standard Transurethral Resection of the Prostate by Each of 4 Private Urologists*

Physician	Total Hospital Cost, $*
MD 1	8,383.67 ± 961.51
MD 2	8,438.34 ± 736.52
MD 3	7,669.17 ± 555.99
MD 4	8,700.47 ± 666.33

*Mean ± standard error of the mean.

TABLE 2.—*Statistical Comparison (P Values, Student's t Test) of Total Hospital Costs to Patients Undergoing Transurethral Resection of the Prostate by Each of 4 Private Urologists**

Physician	MD 1	MD 2	MD 3	MD 4
MD 1	--	>.9	>.5	>.7
MD 2	>.9	--	>.4	>.7
MD 3	>.5	>.4	--	>.2
MD 4	>.7	>.7	>.2	--

*No statistical difference is found in hospital costs between practitioners.

A partial breakdown of these costs shows similar operating room charges incurred by both treatment groups (Table 3). These charges routinely included a $539 fee charged by the hospital for the use of the neodymium:YAG laser. The laser treatment group also incurred an additional supply charge ($840) for the laser delivery fiber. All of the patients undergoing laser prostatectomy were managed as outpatients, however, eliminating any hospital room charges (Table 3). The latter averaged $2,262.96 for patients undergoing standard TURP, who were admitted for a mean and median period of 3.0 days, with a range of 1 to 7 inpatient days (Figure 1). This represented the single largest cost differential between the two treatment groups. No patient in either treatment group in this study required hospital readmission following discharge to home.

Discussion

In this study of patients with symptomatic bladder outlet obstruction due to benign prostatic hyperplasia, treated concurrently and in the same institution by either standard TURP or laser prostatectomy, laser treatment resulted in a net reduction of hospital costs exceeding $2,000. If, based on current Medicare fee schedules, professional fees are estimated to be about $1,000 each for the surgeon and the anesthesiologist, then the total cost to a patient of a TURP performed at Stanford Hospital during the period of this study was more than $10,000. Laser prostatectomy achieved a cost savings of more than 20% of this figure.

These figures represent a conservative estimate of the total cost reduction possible with laser prostatectomy. As noted, the Stanford operating room routinely added a charge for laser use. This serves to offset the initial capital equipment cost and ongoing maintenance costs of the laser to the hospital. No similar charge was added for

TABLE 3.—*Selected Hospital Charges and Total Hospital Costs for Patients Undergoing Standard Transurethral Resection of the Prostate (TURP) and Those Having Laser Prostatectomy*†*

Procedure	OR Charges, $	Laser Fiber, $	Hospital Room Cost, $	Total Hospital Cost, $
TURP	3,003.27	--	2,262.96	8,262.06
Laser	2,971.39	840.00	--	6,174.44

OR = operating room

*P <.0001.
†Mean cost differential, $2,087.62.

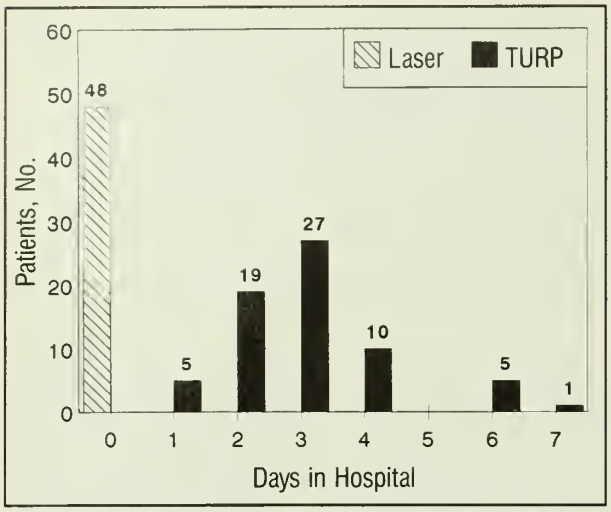

Figure 1.—Distribution of patients by the number of days in hospital required for laser prostatectomy (all outpatient) and for standard transurethral resection of the prostate (TURP) is depicted by bar graph.

the electrosurgical equipment and resectoscopes used for standard TURP. Patients receiving laser treatment were also charged an additional $840 for the price of the disposable laser delivery fiber used to perform laser prostatectomy. Less expensive laser delivery systems are already available on the market, and prices may reach the $400 level by the end of 1995. Reusable laser delivery systems have the potential to cut the cost per case further. A final confounding variable in this analysis is the fact that all patients on the university urology service undergoing laser prostatectomy had preoperative laboratory and radiographic studies done in the hospital, and charges for these were routinely included in their hospital bill. By contrast, most patients undergoing TURP on the community urology service had preoperative studies done at outside facilities, and these were not included as part of their hospital bill. The actual cost of TURP to these patients was, therefore, somewhat higher than the current figures indicate.

Even at the time of this writing, both state and national panels are debating reimbursement for laser prostatectomy and other new surgical approaches to the treatment of benign prostatic hyperplasia. It is possible, and perhaps probable, that physician reimbursement for laser prostatectomy will be set at a lower level than currently provided for TURP. This would, of course, further reduce the total cost of laser prostatectomy relative to TURP, but could be counterproductive if excessively low payment schedules discourage the use of this newer and less costly technology.

A cost that is difficult to quantify is the overall reduction in patient morbidity produced by laser treatment compared with standard electrocautery TURP. Previous studies have documented substantial differences in irrigation fluid absorption, blood loss, and total patient morbidity favoring laser prostatectomy in prospective, randomized trials of these two operative approaches.[9,10] Although our study did not attempt to examine perioperative complications in any detail, transfusion records were readily accessible for all 115 patients. These showed that 12 of 67 patients (18%) undergoing standard TURP received blood transfusions (a total of 18 units). Whereas the direct cost of transfusing a patient was several hundred dollars, the cost of treating even one case of transfusion-related hepatitis or human immunodeficiency virus infection is logarithmically higher. Furthermore, no dollar figure can be assigned to the psychological stress caused to a patient who fears transfusion and its possible complications as he approaches a surgical procedure. No laser-treated patient in our series required a transfusion, and we have now treated more than 250 patients using this technology without using transfusion, including fully anticoagulated patients who would not have been candidates for standard TURP.[15,16]

Similarly, laser prostatectomy has eliminated the occurrence of complications related to intraoperative irrigation absorption, and we and others have not yet seen a case of iatrogenic urinary incontinence result from laser therapy. This condition occurs in perhaps 2% of patients having standard TURP,[3] and individual cases are remarkably costly in terms of surgical correction or the lifelong use of diapers, appliances, or skilled nursing care—not to mention patient disability, both psychic and physical.

Following laser prostatectomy, patients are able to resume all normal physical activities, including returning to work, as soon as the urethral catheter is removed, usually within the first postoperative week. Nonstrenuous work can even be resumed with the catheter in place on the first postoperative day, if the patient so desires. This is unlike the case with standard electrocautery TURP, where common practice dictates only light activity for as long as four to six weeks postoperatively to lessen the risk of straining and late hemorrhage from the prostatic fossa. Thus, laser prostatectomy can result in additional cost savings with fewer workdays missed and with sustained work productivity through the perioperative period for active patients who are not retired.

A final but important consideration in the estimates of the costs of surgical treatment of benign prostatic hyperplasia are retreatment rates. Preliminary data encompassing 18 to 36 months' postoperative follow-up indicate that laser prostatectomy is similar in retreatment rates to standard TURP over this time span.[8,14,23] Long-term follow-up—five and ten years—is clearly indicated to define exact retreatment rates following laser therapy. Laser prostatectomy does appear to produce a substantially lower incidence of postoperative strictures compared with TURP.[9,10,23] Such strictures, representing postoperative scarring of the bladder neck, urethra, or both, are a major cause of reoperation after TURP.

We are currently entering a new era for health care in the United States where the evaluation of new therapies—both medical and surgical—must include assessing not only safety and efficacy, but also relative cost efficiency. Not all of our scientific advances will meet

this final criterion of cost efficiency. In many cases, we may find it most prudent to settle for less advanced technology where relatively small improvements in patient outcomes provided by the latest surgical device or pharmacologic preparation cannot justify the large jumps in cost of care with which they are sometimes associated. This does not appear to be the case with laser treatment of symptomatic benign prostatic hyperplasia. Already shown to be safer and much less morbid than standard TURP, and with notable therapeutic efficacy demonstrated in numerous studies,[4-23] laser prostatectomy also appears to have the potential to substantially undercut the costs associated with standard surgical therapy for this common condition. Using a relatively conservative estimate of $2,500 savings per patient, if 400,000 prostatectomies are done yearly, then the simple introduction of laser technology could eliminate $1 billion from our annual health care budget.

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Conferences and Reviews

Glycemic Control and Complications of Diabetes Mellitus

Discussant
IRL B. HIRSCH, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Dawn E. Dewitt, MD, Chief Medical Resident; Henry Rosen, MD, Professor and Associate Chair; and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

In an illustrative case, a 25-year-old man is seen for further evaluation of his diabetes mellitus. He was diagnosed with insulin-dependent (type I) diabetes mellitus (IDDM) after presenting with diabetic ketoacidosis at age 7. He has had no further hospital stays for his diabetes except for a recent vitrectomy and is currently managed with the daily administration of isophane insulin suspension (NPH) and regular insulin before breakfast. On physical examination, findings were notable for a blood pressure of 140/100 mm of mercury, multiple photocoagulation scars in both eyes, a sinus tachycardia at a rate of 100 beats per minute, poor vibratory sensation to the level of both knees, and trace peripheral edema. Laboratory evaluation reveals a hemoglobin A_{1c} (HbA_{1c}) fraction of 9.2% (normal, 4% to 6%), a serum albumin level of 33 grams per liter (3.3 mg per dl; normal, 35 to 50 grams per liter), and a serum creatinine level of 90 μmol per liter (1.0 mg per dl). Urine studies reveal 1.2 grams per 24 hours of protein with a creatinine clearance of 2.18 ml per second (130 ml per minute).

Background

The morbidity and mortality from IDDM are well appreciated.[1] In a widely quoted survey, 16% of patients with IDDM became blind, 31% died of uremia, and the median life span was 49 years.[2] The Joslin Diabetes Center (Boston, Massachusetts) published similar data, with 40% of patients diagnosed before the age of 20 years dying of uremia.[3] The cause of diabetic microvascular disease has been a subject of controversy. In the 1930s and 1940s, some physicians thought that hyperglycemia was an important predisposing factor. This "glucose hypothesis" was less favored because in some studies muscle basement membrane hypertrophy was thought to represent "an independent and, conceivably, even a primary lesion of the diabetic syndrome."[4] Experimental data from dogs and humans also suggest that insulin deficiency is somehow involved in the pathogenesis of microvascular disease.[5,6] Nevertheless, despite the controversy regarding the origin, there was a growing sentiment that treatment of the hyperglycemia could decrease the consequences of diabetic microangiopathy.[7]

In retrospect, several problems made these issues impossible to resolve. First, before the 1980s, glycemia could be estimated at home only with urine glucose measurements. The addition of occasional laboratory glucose measurements was not useful in a situation of frequent food and activity changes, illness, and emotional stresses. Furthermore, longer-acting insulins were developed 50 years ago to make the management of IDDM more convenient.[8] Many patients were administered one daily injection because this therapy could usually avoid ketosis and hypoglycemia, although patients seemed to do better on multiple administrations.[9] Indeed, the patient in the illustrative case presented here is a reminder of our earlier attempts at insulin therapy: success at preventing metabolic catastrophe, but not at preventing microvascular complications.

Since the discovery of insulin, perhaps the greatest development that improved the ability to manage patients with diabetes mellitus was the introduction of home blood glucose monitoring in the late 1970s and early 1980s. For the first time, patients could accurately measure blood glucose levels at home and make adjustments in their insulin dosage based on their level of glycemia, as opposed to the crude urine glucose testing of the past. Furthermore, researchers, clinicians, and patients for the first time could objectively quantitate overall glycemic control by the measurement of glycosylated hemoglobin fraction. The ability to use these new tools in an attempt to approximate normoglycemia with multiple injections and the newly developed insulin pump were greeted with enthusiasm by many, but not all. Nevertheless, the era of "intensive insulin therapy" was born in 1983 when all of the information to that date was assembled.[10]

In the early 1990s, this therapy was more widely accepted among endocrinologists[11,12] than among the primary care professionals who see most patients with

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ABBREVIATIONS USED IN TEXT

DCCT = Diabetes Control and Complications Trial
HbA_{1c} = hemoglobin A_{1c}
IDDM = insulin-dependent diabetes mellitus
NIDDM = non–insulin-dependent diabetes mellitus

diabetes in the United States.[13] A reason for this discrepancy was the lack of firm evidence that this newer therapy would be effective for preventing or retarding the complications of diabetes. There was also concern that maintaining normal blood glucose levels would result in the occurrence of frequent, dangerous, and unacceptable hypoglycemia.

Diabetes Control and Complications Trial

Rationale and Study Design

With the new ability to achieve normal or near-normal blood glucose levels, reports published in the 1980s tried to address the relationship between glycemic control and diabetic complications. Unfortunately, difficulties in experimental design complicated analysis of the studies. Many of the reports were retrospective, with prospective studies often nonrandomized and with relatively few study subjects. Furthermore, end points for characterizing the complications of diabetes mellitus often lacked precision. Nevertheless, by 1992 evidence was beginning to accumulate that poor glycemic control might be an important factor for the development and progression of diabetic complications.[14,15]

The Diabetes Control and Complications Trial (DCCT) was designed in 1982 and 1983 to ascertain whether intensive therapy for IDDM, directed at achieving blood glucose levels as close to the nondiabetic range as possible, would have a different effect on the incidence of diabetic complications than standard therapy. Given that it is not possible to prospectively assign a large number of patients different goals for glycemic control, the study was designed to test the differences in therapeutic programs, as opposed to differences in glycosylated hemoglobin levels.

The DCCT addressed two fundamental questions, the first relating to primary prevention. That is, in patients without any evidence of microvascular disease, could intensive therapy prevent its development? The second question concerned intervention. In patients with evidence of early microangiopathy, could intensive therapy prevent its progression? Retinopathy was the major end point because of its known epidemiology and relative ease in assessment. Therefore, persons in the primary-prevention cohort were required to have their IDDM for fewer than five years and to have no evidence of any diabetic retinopathy. Those in the secondary-intervention group were eligible if they had had their diabetes for less than 15 years and had minimal or moderate nonproliferative retinopathy. Early albuminuria (< 200 mg per day) was also allowed in this group, but was not required for study entry. By 1985, there were 29 centers in the United States and Canada participating, and they would eventually enroll a total of 1,441 subjects. All patients were between 13 and 39 years old when they were randomly assigned to intensive ("experimental") or conventional ("standard") therapy.

Conventional therapy was designed to mimic standard diabetes care in the community. These subjects administered insulin (intermediate and rapid-acting) once or twice a day, self-monitored urine or blood glucose levels daily (at the beginning of the study, only urine glucose testing was done), and received education about diet and exercise.[16] Subjects did not generally supplement insulin based on glucose monitoring. The primary clinical goals were to avoid the development of symptomatic hyperglycemia, frequent hypoglycemia, or ketonuria and to maintain normal growth, development, and ideal body weight. Women who became pregnant or were planning a pregnancy received intensive therapy until the time of delivery, after which they resumed conventional therapy. These subjects were seen in their clinics quarterly, and for this cohort, both patients and investigators were blinded to the women's hemoglobin A_{1c} levels.

Intensive therapy was designed to achieve normal blood glucose levels by administering at least three injections of insulin a day or by an insulin infusion pump. Subjects could switch back and forth from several injections to a pump if desired. Insulin doses were adjusted on a daily basis determined by a minimum of four daily home blood glucose measurements, dietary intake, and anticipated exercise. Glycemic goals included premeal glucose levels of between 3.9 and 6.67 mmol per liter (70 and 120 mg per dl), postprandial concentrations of less than 10.0 mmol per liter (180 mg per dl), and at least one weekly 3 AM measurement greater than 3.6 mmol per liter (65 mg per dl). The goal for the HbA_{1c} fraction was below 6.05%, as this was the upper limit of the normal range. Subjects had HbA_{1c} levels measured monthly at their clinic visits, and these were available for review by both the patients and the investigators. Subjects were often admitted to hospital to initiate intensive therapy and had frequent telephone contact between visits to review blood glucose records, if necessary.

Diagnosis of the primary end point, retinopathy, was based on seven-field stereoscopic fundus photographs taken every six months and assessed by graders unaware of the treatment-group assignments. The overall levels of severity of retinopathy were determined for each patient according to the Early Treatment Diabetic Retinopathy interim scale (Table 1).[17] Progression of the retinopathy was defined as a three-step change from baseline.

Other end points included nephropathy, neuropathy, and severe hypoglycemia. Nephropathy, which was assessed by annual timed urine collections for measuring urine albumin levels and creatinine clearance, supplemented by a more sensitive measure of the glomerular filtration rate, the iothalamate sodium I 125 clearance test. This test was initiated three years into and at the termination of the study. Microalbuminuria and clinical-grade albuminuria were defined as albumin excretion

TABLE 1.—*Retinopathy Grading Scale Used in the Diabetes Control and Complications Trial**

Step	Level of Retinopathy	Eligibility
1	No retinopathy	Primary prevention
2	Microaneurysms, one eye	Secondary intervention
3	Microaneurysms, both eyes	Secondary intervention
4-5	Mild NPDR	Secondary intervention
6-9	Moderate NPDR	Secondary intervention
10-13	Severe NPDR	
14-15	Mild PDR	
16-17	Moderate PDR	
18-25	High-risk PDR and worse	

NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy

*From the Diabetes Control and Complications Trial Research Group.[19]

rates between 40 and 300 mg per 24 hours (27 and 201 μg per minute) or 300 mg per 24 hours and higher (201 μg per minute or higher), respectively. Neuropathy evaluations were based on a standard neurologic history and physical examination conducted by a specialist; nerve conduction studies in the median, peroneal, and sural nerves; and autonomic nervous system testing. Clinical neuropathy was defined as abnormal findings on physical examination consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic nervous system responses to testing. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and that was associated with either a blood glucose level below 2.8 mmol per liter (50 mg per dl) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.[18]

Study Results

Glycemic Control

The entire study group of 1,441 subjects was observed for an average of 6.5 years (range, 3 to 9) for a total of 9,300 patient-years.[19] Significant differences in HbA_{1c} levels were maintained after baseline between the intensive-therapy and conventional-therapy groups in both cohorts ($P < .001$).[19] Less than 5% of patients in the intensive-therapy group maintained a normal glycosylated hemoglobin level throughout the study, while 44% of this group achieved this goal at least once. Quarterly seven-point capillary blood glucose profiles revealed mean (± standard deviation) values of 155 ± 30 mg per dl versus 231 ± 55 mg per dl for the intensive- and conventional-therapy groups, respectively ($P < .001$).

TABLE 2.—*Risk Reduction of Retinopathy With Intensive Therapy*

Outcome	Risk Reduction, %
Primary prevention	
≥1 Microaneurysm	27
≥3-Step progression	60
Sustained 3-step progression	76
Secondary intervention	
≥3-Step change	34
Sustained ≥3-step change	54
Proliferative or severe nonproliferative retinopathy	47
Laser treatment	56

Retinopathy

In the primary-prevention cohort, after five years' duration, the cumulative incidence of retinopathy in the intensive-therapy group was about 50% less than in the conventional-therapy group. The risk of the development of at least one microaneurysm was reduced by 27%, a single three-step progression by 60%, and sustained worsening of retinopathy by 76% in the primary prevention group (Table 2). Conclusions for more severe forms of retinopathy (proliferative and severe nonproliferative retinopathy or clinically important macular edema) could not be drawn because there were too few subjects in this group. In the secondary-intervention group, intensive therapy decreased a three-step progression by 54%, while reducing the incidence of proliferative or severe nonproliferative retinopathy and the need for laser therapy by 47% and 56%, respectively (Table 2). Patients in the intensive-therapy group had a higher cumulative incidence of sustained progression of retinopathy by three steps or more during the first year than did those in the conventional-therapy group, but a lower cumulative incidence beginning at 36 months and continuing for the rest of the study. As a secondary analysis, the relationship between the progression of retinopathy and HbA_{1c} levels was determined (Figure 1). This analysis showed a continuously increasing risk of sustained progression by three steps with increasing mean HbA_{1c} values.

Nephropathy

In both cohorts, microalbuminuria and clinical-grade albuminuria developed in fewer patients in the intensive-therapy group. Intensive therapy decreased the risk of microalbuminuria by 34% in the primary-prevention group and by 44% in the secondary-intervention cohort. The incidence of clinical-grade albuminuria was decreased by 43% (not significant) and 56% in the primary-prevention and secondary-intervention groups, respectively (Table 3).

Neuropathy

The treatment effect of intensive therapy was similar for neuropathy. Intensive therapy decreased the risk of clinical neuropathy for the primary-prevention and the secondary-intervention groups by 69% and 57%, respectively. The combined cohorts had a 60% risk reduction with intensive therapy. Individually, each component of the clinical neuropathy definition was reduced with

TABLE 3.—*Risk Reduction of Nephropathy With Intensive Therapy**

Outcome	Risk Reduction, %	P
Primary prevention		
UAE ≥40 mg/day (27 μg/min)	34	.04
UAE ≥300 mg/day (201 μg/min)	43	NS
Secondary intervention		
UAE ≥40 mg/day (27 μg/min)	44	.001
UAE ≥300 mg/day (201 μg/min)	56	.001
Both cohorts		
UAE ≥40 mg/day (27 μg/min)	39	≤.002
UAE ≥300 mg/day (201 μg/min)	54	<.04

NS = not significant, UAE = urinary albumin excretion

*Adapted from the Diabetes Control and Complications Trial Research Group.[19]

intensive therapy (examination, $P < .001$; autonomic nerve study, $P = .04$; nerve-conduction study, $P < .001$).

Macrovascular Disease

When combining all major cardiovascular and peripheral vascular events, intensive therapy reduced the risk by 41%, although this was not significant. Intensive therapy also reduced the development of hypercholesterolemia (defined as a low-density-lipoprotein-cholesterol level > 160 mg per dl) by 34%, but had no effect on the development of hypertriglyceridemia or hypertension.

Adverse Events and Safety

Mortality did not differ between the two treatment groups. In all, 11 subjects died, 7 of whom were in the intensive-therapy group. The event rates for diabetic ketoacidosis were similar in the two groups. The incidence of severe hypoglycemia was about three times higher in the intensive-therapy group than in the conventional-therapy group (Table 4). There were no deaths, myocardial infarctions, or strokes definitely attributable to hypoglycemia. Secondary analysis regarding the rate of severe hypoglycemia and increased HbA_{1c} fraction showed that the risk of severe hypoglycemia increased continuously with lower glycosylated hemoglobin values (Figure 1). Weight gain, another adverse event, was more prevalent with intensive therapy. At five years, patients receiving intensive therapy had gained a mean of 4.6 kg (10 lb) more than patients receiving conventional therapy. Finally, neuropsychological and quality-of-life testing did not show any differences between the two treatment groups. The added demands of intensive therapy in addition to the increased frequency of severe hypoglycemia in this group did not lead to any neurobehavioral changes.

Recommendations

It should again be noted that the DCCT was intended to ascertain if different forms of therapy for IDDM alter the natural history of diabetic complications. The data on

TABLE 4.—*Severe Hypoglycemia in the Diabetes Control and Complications Trial Combined Cohort*

Level of Hypoglycemia	Episodes/100 Patient-Years: Intensive Therapy	Episodes/100 Patient-Years: Conventional Therapy	Risk Ratio
Severe	62	19	3.3
Coma or seizure	16	5	3.0
ED or hospital admission	9	4	2.3
Deaths	0	0	--

ED = emergency department

glycemic goals for individual patients should be extrapolated with at least some caution because this was not the study design. Still, the results are conclusive and dramatic. Intensive therapy for IDDM resulting in a mean HbA_{1c} fraction of 7.2% compared with conventional therapy with a mean HbA_{1c} of 8.9% delays the development and slows the progression of diabetic retinopathy, nephropathy, and neuropathy by 35% to 70%. The major risk, however, severe hypoglycemia, was three times more common with intensive therapy. This is critical because DCCT study subjects had many more interactions with their health care teams than most patients with IDDM in the country.* In addition, this was a relatively homogeneous patient group, and thus conclusions generalized to all patients with diabetes mellitus need to be made with caution. Nevertheless, certain recommendations are now warranted.

The DCCT study group recommended that most patients with IDDM be treated with closely monitored intensive regimens with the goal of maintaining glycemia "as close to the normal range as safely possible."[19] This goal will need to be individually tailored because for many patients the risk-to-benefit ratio may not favor normoglycemia. The most obvious example are patients who are unaware they have hypoglycemia or who have a history of repeated episodes of severe hypoglycemia. An increasing number of patients seem to be attempting to achieve normal or near-normal levels of glycemia despite the risk of dangerous and occasionally life-threatening hypoglycemia. These patients need to be strongly encouraged to increase their glycemic targets. It is hoped that new strategies to combat this problem will be forthcoming.[20,21]

The DCCT study group also recommended that the data should not be extrapolated to apply to patients with advanced complications such as end-stage renal disease or cardiovascular or cerebrovascular disease.[19] Unfortunately, improved glycemic control does not appear to be effective in treating advanced retinopathy[22] or nephropathy.[23,24] Similarly, repetitive and severe hypoglycemia appears to be too risky for patients with substantial macrovascular disease. Improved control still may be protective for one type of complication

*See also the editorial by D. M. Nathan, MD, "Management of Diabetes Mellitus After the DCCT—What's Next?" on pages 469-470 of this issue.

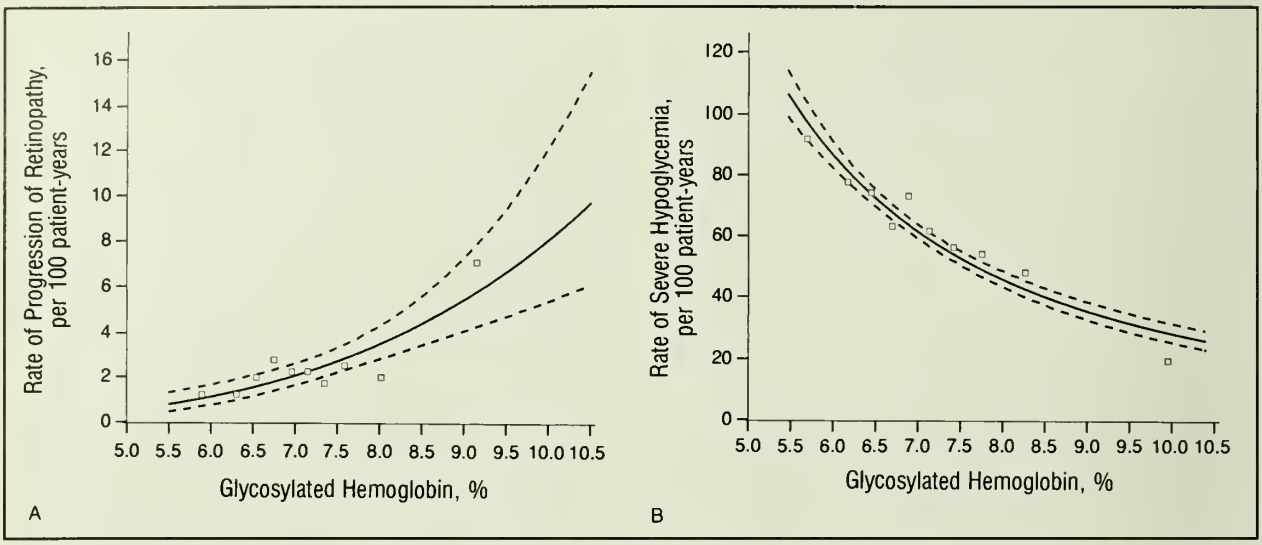

Figure 1.—**A**, The risk of sustained progression of retinopathy and (**B**) the rate of severe hypoglycemia in the patients receiving intensive therapy, according to their mean glycosylated hemoglobin values during the trial, are shown. A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least 3 steps from baseline that was sustained for at least 6 months. In **A**, the glycosylated hemoglobin values used were the mean of the values obtained every 6 months. In **B**, the means of the monthly values were used. Open squares indicate the crude rates within deciles of the mean glycosylated hemoglobin values during the trial; each square corresponds to more than 400 patient-years. The lines are regression lines estimated as a function of the log of the mean glycosylated hemoglobin value in **A** and the log of the glycosylated hemoglobin value in **B**; the dashed lines are the 95% confidence intervals (reprinted with permission from *The New England Journal of Medicine*[19]).

after another one has developed, however. A variety of psychological benefits stem from improved glycemic control.[25,26]

Conclusions regarding the effects of intensive therapy should also be made with caution for children younger than 13 years.[19] Children below this age were not included in the study, and the evidence to date suggests that the contribution of the prepubertal years of diabetes mellitus to chronic complications may be minimal.[27]

Perhaps the greatest debate regarding the DCCT is how these data should be extrapolated to patients with non–insulin-dependent (type II) diabetes mellitus (NIDDM). Data to date certainly support an association of hyperglycemia with the presence or progression of complications in NIDDM.[28-31] Although it appears that the degree of hyperglycemia, not the type of diabetes, best predicts the development or progression of retinopathy and nephropathy, we are still awaiting the results of two prospective interventional studies in this patient population.[32,33] The DCCT study group and others have recommended caution in extrapolating the data to patients with NIDDM,[19,34,35] whereas the group at the National Institutes of Health has been less conservative.[36] There appears to be general agreement that for patients with NIDDM, it is most desirable that meticulous glycemic control be maintained through diet and exercise alone. Most patients will eventually require an oral hypoglycemic agent to maintain similar metabolic control. Preliminary data from the United Kingdom Prospective Diabetes study indicate that in 83% of patients with newly diagnosed NIDDM, treatment with diet alone fails within a year, and the patients require drug therapy.[37]

The controversy arises when exogenous insulin is required. After five years, only about half of patients who initially had excellent or good glycemic control with an oral agent still have a favorable response.[38] Evidence is accumulating that insulin may directly promote atherosclerosis.[39] Furthermore, it has been understood since the discovery of insulin that obese patients with NIDDM gain even more weight when started on insulin therapy.[9] Insulin administration for 3 to 12 months in these patients produces a mean weight gain of 6 kg (13 lb).[40] Certainly, improved glycemic control with the addition of a sulfonylurea may also cause weight gain.[37] In its position statement, the American Diabetes Association states that "there is no reason to believe that the effects of better control of blood glucose levels would not apply to people with NIDDM."[41(p1556)] It is also stressed that glycemic goals need to be tailored to each patient, especially older patients in whom severe hypoglycemia could have more devastating consequences (such as cardiovascular complications) than seen in the younger patients with IDDM studied in the DCCT.[41]

The DCCT results should also not be extrapolated to other forms of therapy that attempt to achieve normal blood glucose levels. For example, implantable insulin pumps, glucose sensors operating in conjunction with an internal or external insulin pump, and implanted microencapsulated islets will all have their own advantages and disadvantages.[42] Risk-to-benefit ratios with intensive therapy for IDDM should not be compared with those of the newer, as yet unproven, therapeutic strategies. Similarly, the DCCT results should not be interpreted as an endorsement for pancreas transplanta-

tion. Even though there have been some encouraging data regarding the beneficial effects of pancreas transplantation on neuropathy and nephropathy (but not retinopathy),[43,44] this form of therapy requires lifelong immunosuppression and cannot be recommended as a routine treatment modality.[45]

Implications

Medical Implications

The DCCT was not designed to study the effects of different levels of glycosylated hemoglobin on microvascular complications. The DCCT investigators realized it would not be possible to prospectively assign patients to different glycemic goals. Rather, the trial was undertaken to study the effects of two different treatment regimens (intention-to-treat study). Nevertheless, the secondary analyses comparing the progression of retinopathy and severe hypoglycemia with the levels of HbA_{1c} were impressive.

Another issue the DCCT addressed is the possibility that there is a threshold level of hyperglycemia where the progression of retinopathy appeared. In the secondary analysis, it was shown that at each increased level of HbA_{1c}, the progression of retinopathy increased in a curvilinear relationship (Figure 1). Stated differently, any sustained decrease of HbA_{1c} will decrease the risk of retinopathy to progress. This is encouraging because less than 5% of the subjects in the DCCT maintained their HbA_{1c} levels within the normal range. Although levels of glycemic control established in the DCCT may be difficult to achieve, there are still benefits even if blood glucose levels are not "normalized." The secondary analyses for albuminuria and neuropathy are not yet available, but will be reported in the future.

The DCCT confirmed the results of other trials revealing a transient worsening of retinopathy with intensive therapy.[46,47] These retinal changes consisted of the development of soft exudates or intraretinal microvascular abnormalities in 22% of the intensive-therapy group compared with 13% of the conventional-therapy group of the secondary-intervention cohort during the first year. Because the abnormalities generally disappeared by 18 months, the DCCT study group recommends that the worsening of retinopathy should not deter clinicians from using intensive therapy.[19] Subjects with early worsening had a 74% reduction in the risk of subsequent progression compared with patients with early worsening who received conventional therapy. It should be pointed out that the DCCT did not study patients who at randomization had severe nonproliferative retinopathy or mild proliferative retinopathy. Conclusions about transient worsening of retinopathy in these patients are not possible, and physicians will have to proceed with caution with this group.

Another adverse effect of intensive therapy, weight gain, was an early observation from the DCCT.[48] Several studies have shown that patients with IDDM will gain about 5 kg (11 lb) during the first year of intensive therapy.[48-50] It has recently been shown that 70% of weight gain with intensive therapy could be accounted for by the elimination of glycosuria and 30% by the reduction of energy expenditure.[51] Follow-up of the DCCT patients over the next decade will help determine the effects of this extra weight, especially with regard to cardiovascular disease. It is hoped that the benefit of intensive therapy will outweigh the adverse effects of weight gain by reducing the incidence of diabetic nephropathy, the major risk for early death in patients with IDDM.[2] Neither the clinical importance of this weight gain nor its mechanism should be extrapolated to patients with NIDDM.

The most worrisome medical implication of the results of the DCCT is the increased risk of hypoglycemia. Previous estimates suggest that patients with IDDM may have 2,000 to 4,000 symptomatic episodes of hypoglycemia over a 40-year span.[52] Furthermore, approximately 4% of patients with IDDM die of hypoglycemia.[52] Because these data are based on conventional therapies of the past, how will the epidemiology of this event, with its associated morbidity and mortality, change with intensive therapy? In the DCCT, a threefold increase in the incidence of severe hypoglycemia occurred with the imperfect (yet improved) insulin replacement regimens of multiple administrations and insulin pumps. This increase occurred despite the frequent patient interactions with an expert team of diabetologists, nurses, nutritionists, and behavioral specialists who sought to minimize the frequency of hypoglycemia. How common will severe hypoglycemia be in the context of intensive therapy in a conventional venue, be it a physician's office, a university-based clinic, or a health maintenance organization? Both the DCCT Research Group and the American Diabetes Association caution that intensive therapy may not be appropriate for all patients, especially those who are unaware when they have hypoglycemia.[19,41] Patients who are unable or unwilling to monitor blood glucose levels regularly should not be encouraged to achieve normal blood glucose concentrations. Nevertheless, the devastating microvascular complications that appear to be due to hyperglycemia[36] lead to a risk-to-benefit ratio that favors intensive therapy for most patients with IDDM.[19,34-36,41]

The other immediate medical problem that both practitioners and patients need to understand is the lack of standardization of glycosylated hemoglobin assays. In the DCCT, HbA_{1c} levels were measured by a central laboratory with a nondiabetic range of 5.05% ± 0.5%. Unfortunately, a variety of methods (and normal ranges) are used for measuring glycosylated hemoglobin, and thus physicians should not directly extrapolate DCCT HbA_{1c} concentrations as targets for their patients. Although it is now possible for clinical laboratories to standardize this important measurement,[53] few do so.

Social Implications

The overall cost of diabetes mellitus in 1992 was $91.8 billion, of which half was due to direct costs.[54]

Much of this cost is for the care of the complications. Direct inpatient care costs for chronic complications were $9.7 billion.[54] The total cost of diabetes has more than quadrupled since 1987.[54] Intensive therapy is about two to three times more expensive than conventional therapy, primarily due to supplies. Blood glucose strips alone, at about $0.50 each, are too expensive for many patients. Over a one-year period, glucose strips could cost $730 for patients who practice intensive therapy and measure their blood glucose concentrations four times a day. Being monitored by diabetes clinical nurse specialists and nutritionists would be an added expense for many. Although the results of the DCCT are dramatic, is implementation affordable in our struggle for reducing the costs of health care? A cost-benefit analysis should be released in the near future to address this question. It may be that intensive therapy for IDDM will be an excellent investment because of the financial savings of preventing or retarding the development of complications.

While we are awaiting the cost-benefit analysis, how are we to afford this therapy, given the constraints of managed care? For primary care physicians on a capitated budget, managed care has been described as a "powerful disincentive to quality care for patients with diabetes."[55] One of our major challenges should be to determine how we can treat diabetes at an intensity to yield outcomes similar to those shown in the DCCT but in the most cost-efficient manner possible. Further studies for many chronic diseases are clearly needed in this area.

Another important issue that requires review concerns the effects of the general attitudes and practice behaviors of primary care physicians who treat patients with IDDM. Primary care physicians' attitudes may help patients achieve good glycemic control.[56-58] Attitudes are not enough, however. Physicians also need a basic understanding of how to achieve maximal glycemic control. Unfortunately, a recent survey concluded that "primary care physicians are not fully aware of recommended criteria for intensive treatment of blood glucose in IDDM."[13(p765)] In this survey of general practitioners, family physicians, and internists, fewer than half of respondents thought that achieving the target glycosylated hemoglobin fraction was important, 38% routinely used a dietitian and nurse educator, and only 50% recommended two or more daily injections to manage IDDM.[13] Other recent reports have shown similar major deficiencies in the practice behaviors of primary care physicians.[59-62] The importance of these data cannot be overemphasized because in a recent survey, 96% of outpatient visits for primary care by patients with diabetes were made to general and family practitioners and internists.[63] Our fundamental challenge, therefore, is to provide intensive therapy for the large number of people in this country with IDDM who could benefit from it. Unfortunately, most physicians lack the training to provide this therapy. Because many of these primary care physicians—general internists, family physicians, general pediatricians—each has only a few patients with IDDM who would require intensive therapy (at least as carried out in the DCCT), it would not be cost- or time-efficient to provide this intensity of service.[36] A typical primary care practice is likely to have fewer than ten patients with IDDM.[64,65] Therefore, ideally many of these patients should be referred to centers with the expertise for this level of therapy, providing there is adequate collaboration with the referring physician.[36,66] At the very least, there needs to be a greater emphasis on continuing medical education about diabetes-related topics for primary care physicians[13,67] and physicians in training. The controversy of who is best suited to care for patients with diabetes mellitus is not new,[68] but as fewer young physicians are choosing endocrinology as a career,[69] family physicians, general internists, and pediatricians will have a greater role in providing primary care for these patients.

Several models of diabetes care have recently been developed that try to address these problems. In one model, which would be more appropriate for patients with IDDM, the "diabetes intensive management team" would provide all primary care.[70] Although this team would usually include a diabetologist, any physician could lead this team as long as he or she had developed the appropriate skills. With this model, it also may be appropriate to have a different provider manage non–diabetes-related problems. For patients with NIDDM, the model could be altered so that the diabetes team is used as often as deemed necessary by the primary care provider. For these models to be effective, communication must be adequate so that care can be integrated.[70]

Another evolving model for diabetes management in a primary care setting is "staged diabetes management."[64,71] In this setting, practice guidelines are developed for a particular community and clinical pathways (decision paths) are developed both for IDDM and NIDDM. In addition, detailed narratives and flowcharts allow a primary care provider to initiate, adjust, and maintain treatment. Specific criteria have been developed for referral to an endocrinologist. Initial results of staged diabetes management are encouraging,[71] and further research will be welcomed.

Finally, few patients and their physicians have the support of nurses, dietitians, and behavioral scientists such as were available to the DCCT patients. Unfortunately, the concept of the "diabetes team" is poorly understood.[67] Acknowledging that the center of any team is the patient, we should better use other team members as "physician extenders."[72] In the DCCT, most of the patient interaction was not with the physician, but with these other team members. Placing the emphasis of diabetes care with these other highly qualified personnel, with a physician supervising, is also more cost-efficient. This treatment strategy was dramatically successful in reducing the incidence and progression of microvascular complications in the DCCT. It is now time to implement this therapy for all appropriate patients.

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Role of Nitric Oxide in Insulin-Dependent Diabetes Mellitus–Related Vascular Complications

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Patients with insulin-dependent diabetes mellitus are at high risk for vascular disorders such as hypertension, nephropathy, and retinopathy. The most common cause of morbidity and mortality in patients with insulin-dependent diabetes is vascular disease. Despite ongoing research, the pathogenesis of vascular disease in diabetes remains unclear. In recent years, numerous investigators have examined the role of the endothelium-derived relaxing factor, nitric oxide, in the disease state of hypertension and its complications. We review the role of nitric oxide in the development of diabetes-related vascular disease and discuss findings suggesting that nitric oxide metabolism and vascular responsiveness to nitric oxide are altered in diabetes. Patients with diabetes may benefit from therapy that addresses this pathogenic deficiency.

(Traub O, Van Bibber R: Role of nitric oxide in insulin-dependent diabetes mellitus–related vascular complications. West J Med 1995; 162:439-445)

Over the past decade, considerable research has provided insight into the identity, function, and pharmacology of the endothelium-derived relaxing factor (EDRF). The consensus is that the vasoactive substance is the short-lived reactive compound, nitric oxide. More recently, two classes of nitric oxide synthase enzymes have been characterized. The first is a constitutive, calcium ion (Ca^{2+}) and calmodulin-dependent isoenzyme that, in healthy vessels, releases small amounts of nitric oxide from endothelial cells in response to agonist stimulation or shear stress. Agents such as acetylcholine, bradykinin, and serotonin require an intact endothelium to elicit part or all of their vasodilation. It appears that each shares a common mechanism beginning with a membrane receptor-mediated increase in intracellular calcium in vascular endothelial cells. This rise in intracellular Ca^{2+} results in the Ca^{2+}-calmodulin–dependent activation of the enzyme complex, nitric oxide synthase. Concurrent with the oxidation of the reduced form of nicotinamide-adenine dinucleotide phosphate, this complex converts L-arginine to L-citrulline and releases a molecule of nitric oxide. This short-lived compound diffuses directly into the vascular smooth muscle cell and activates guanylate cyclase through reaction with its heme group, in turn causing an increase in intracellular cyclic guanosine monophosphate (cyclic GMP) levels in the smooth muscle cell. Cyclic GMP acts on sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase (ATPase) mechanisms to promote the resequestration of intracellular Ca^{2+} into internal stores and hence causes relaxation of smooth muscle (Figure 1; see review[1]).

The other important class of nitric oxide synthase involves a cytokine-inducible, Ca^{2+}-calmodulin–independent isoform that releases large amounts of nitric oxide for extended periods.[2] The likely biologic effect is the elimination of tumor cells, bacteria, and parasites primarily by binding to and destroying iron-containing enzymes.[2,3] This inducible isoform was originally described in macrophages, but subsequently has been found in most vascular cells as well.

Certain vascular disorders have been suggested to occur as a result of a pathologic alteration in either major isoform. For example, an interruption in the constitutive-release pathway has been implicated in hypertension, whereas an overproduction of nitric oxide from the inducible-release pathway has been implicated in the severe hypotension of septic shock. The constitutive nitric oxide synthase has also been found in platelet cytosol, where it may act as part of a negative-feedback mechanism to regulate platelet aggregation through cyclic GMP. Nitric oxide production has also been detected in the nervous system, hepatocytes, neutrophils, and other cells, whereas its full biologic role remains to be elucidated.[2]

The incidence of vascular diseases such as hypertension, atherosclerosis, nephropathy, and retinopathy is higher among patients with diabetes than in the general population.[4-7] Thus, the risk of myocardial infarction,

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
cyclic GMP = cyclic guanosine monophosphate
EDRF = endothelium-derived relaxation factor
IDDM = insulin-dependent diabetes mellitus

cerebrovascular accidents, renal failure, and blindness is increased. Other common complications seen in persons with diabetes with peripheral vascular disease include impotence and abnormalities in clotting factors that may increase the risk of infarct and ischemia-related damage.[8,9] More advanced cases of peripheral vascular disease can result in amputation of the lower extremities due to vascular insufficiency (Table 1).[4-10] Altered blood vessel function is the common factor among these vascular complications. Blood vessels from persons with diabetes show many of the structural and functional alterations characteristic of the vessels of persons with hypertension, including vascular hypertrophy and an increased sensitivity to normal stimuli.[11] Because a lack of endothelium-derived nitric oxide has already been implicated in hypertension,[12] it is reasonable to suspect that alterations in nitric oxide metabolism may contribute to vascular complications associated with diabetes.

In this review, we discuss alterations in nitric oxide metabolism and efficacy that are associated with diabetic or hyperglycemic conditions. Abnormalities in the endothelium, intercellular diffusion, and smooth muscle cells are considered. It has generally been thought that the disorders stem from problems with the constitutive nitric oxide release pathway, and research has been directed with this in mind. It may be presumptuous, however, to assume that alterations in the inducible nitric oxide release pathway do not contribute to the vas-

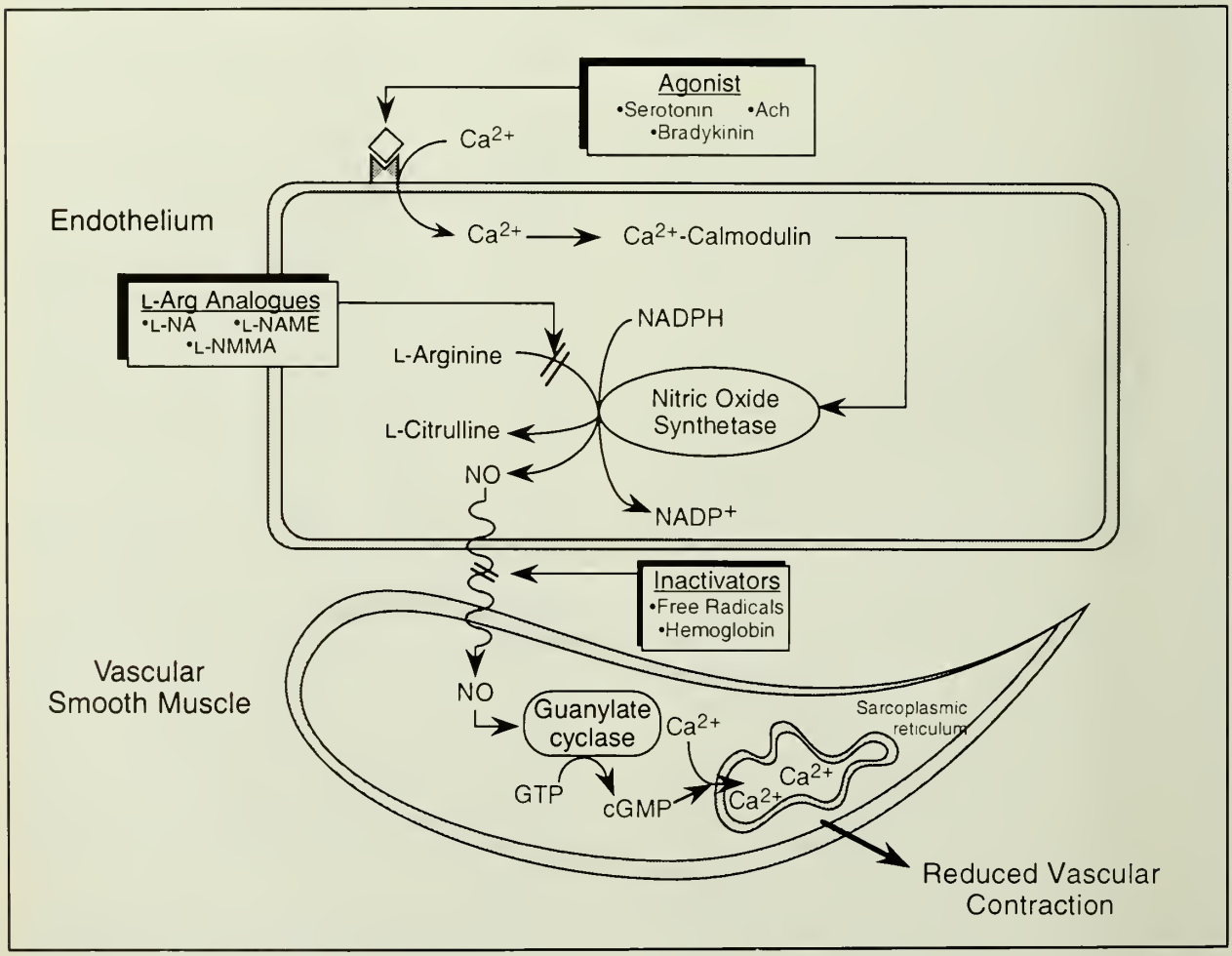

Figure 1.—The metabolic pathways of the endothelium-derived relaxing factor, nitric oxide (NO) are shown. Agonists that cause a rise in intracellular calcium (Ca^{2+}) activate the NO synthetase enzyme through Ca^{2+}-calmodulin dependent activation. NO diffuses into smooth muscle cells, causing a rise in cyclic guanosine monophosphate (cGMP), which leads to the resequestration of Ca^{2+} into internal stores and results in vasodilation. Nonmetabolizable analogues of arginine—L-nitroarginine (L-NA), L-nitromonomethyl arginine (L-NMMA), and L-nitroarginine methyl ester (L-NAME)—inhibit NO production. Reactive compounds (heme, free radicals) may act to degrade NO. Ach = acetylcholine, GTP = guanosine triphosphate, L-Arg = L-arginine, $NADP^+$ = the oxidized form of nicotinamide-adenine dinucleotide phosphate, NADPH = the reduced form of NADP

TABLE 1.—*Insulin-Dependent Diabetes Mellitus–Associated Vascular Complications*

Vascular Complication	*Consequences*	*Review or Reference*
Hypertension.....	Myocardial infarction, cerebrovascular accident	Anderson and Rocchini, 1993[4]
Hyperlipidemia or cholesterolemia ..	Atherosclerosis	Walker, 1993[5]
Nephropathy.....	Renal failure	Breyer, 1992[6]
Retinopathy.....	Blindness	Rosenbloom, 1983[7]
Clotting abnormalities....	Infarct or ischemia	Maiello et al, 1988[9]
Other peripheral vascular disease..	Impotence, amputation of extremities	Maatman et al, 1987[8]; Falkenberg et al, 1990[10]

cular complications associated with insulin-dependent diabetes mellitus (IDDM).

Nitric Oxide and Insulin-Dependent Diabetes Mellitus

Gross Alteration in the Endothelium

Several studies report a change in endothelial integrity in diabetes. Independent investigators have shown that endothelial injury is associated with factors related to poor serum glucose regulation in patients with diabetes. Substantially higher levels of endothelial vascular desquamation have been reported in patients with IDDM, and it has been suggested that hyperglycemic conditions may be responsible.[13] Increased levels of nonenzymatic glycosylation occur in vivo for endothelial cells from rats with streptozocin (formerly streptozotocin)-induced diabetes,[14] a factor that may contribute to altered endothelial integrity.

Other studies report that the growth and migration of endothelial cells are inhibited with hyperglycemia. Free radicals generated by the auto-oxidation of glucose may delay endothelial cell replication time in vitro.[15] It remains to be seen whether this phenomenon occurs in vivo, although in one study, it was suggested that hyperglycemic conditions facilitate the sulfhydryl oxidation of serum proteins and contribute to the inhibition of endothelial cell proliferation in bovine carotid arteries.[16] The hypothesis that the depletion of antioxidants observed in diabetes[17] acts to complicate this factor is supported by studies in which the antihypertensive effect of exogenous antioxidant agents has been reported in patients with diabetes[18] and by a study that reported that EDRF was restored in diabetic rat aorta by superoxide dismutase.[19]

Another study showed inhibited migration of endothelial cells in hyperglycemic conditions.[20] This effect persisted even when cells were reincubated in physiologic concentrations of glucose, suggesting that irreversible damage may occur even when serum glucose levels are tightly regulated in a diabetic subject. The presence of L-fucose, a monosaccharide observed to be present at higher levels in diabetes, has also been associated with an inhibited proliferation of cultured endothelial cells.[21]

The general scheme portrayed in these studies is that endothelial damage in diabetic subjects is further complicated by hyperglycemia-induced impairment of endothelial proliferation and migration. This defect in endothelial repair may ultimately affect nitric oxide production and release from these cells.

Changes in Endothelial Metabolism

Both persons with diabetes and experimental models of diabetes show an impairment in endothelial-dependent relaxation of smooth muscle. In one study acute and chronic hyperglycemia almost completely suppressed the acetylcholine-induced vasodilation in arteries from rats with streptozocin-induced diabetes, but caused no impairment in the relaxation due to sodium nitroprusside—an endothelium-independent vasodilator.[22] These data suggest a defect in either the production or release of nitric oxide from endothelial cells.

The increased level of the monosaccharide, L-fucose, in diabetes has also been implicated in altered *myo*-inositol transport. L-Fucose has been found to competitively inhibit the uptake of *myo*-inositol into endothelial cells.[21] A reduction in the level of *myo*-inositol would be expected to reduce phosphoinositide-mediated calcium release from intracellular stores, hence interfering with the Ca^{2+}-dependent nitric oxide generation.

Impaired EDRF-mediated vasodilation, which has particular clinical relevance to diabetes, has been characterized in several articles. One study showed considerable impairment of acetylcholine-induced vasodilation in the corpus cavernosum of diabetic rabbits when compared with control groups.[23] The corpus cavernosum of hypercholesterolemic rabbits also showed reduced dilation in response to acetylcholine in a separate experiment by the same laboratory.[24] Alteration in lipid metabolism and subsequent or independent deficiency in EDRF-mediated vasodilation may therefore be contributing factors to the pathogenesis of impotence often noted in persons with diabetes.

Researchers have demonstrated that advanced glycosylation end products inactivate nitric oxide activity and that their reactivity was present at high levels in atherosclerotic plaques in vessels from patients with diabetes.[25] Other studies showed that EDRF-mediated vasodilation in the hindquarters of streptozocin-treated rats was particularly dependent on nitric oxide and that there was considerable impairment of nitric oxide synthesis and, therefore, blood flow in vessels from the hindquarters of these rats.[26] This observation may be relevant to the clinical finding that advanced vascular disease in the lower extremities often results in amputation of a foot or both feet of many diabetic patients.[10] Other studies suggest that nitric oxide dysfunction in the eyes[27] and brain[28] may be responsible for the pathogenesis of ophthalmic complications and the incidence of stroke commonly seen in diabetes.

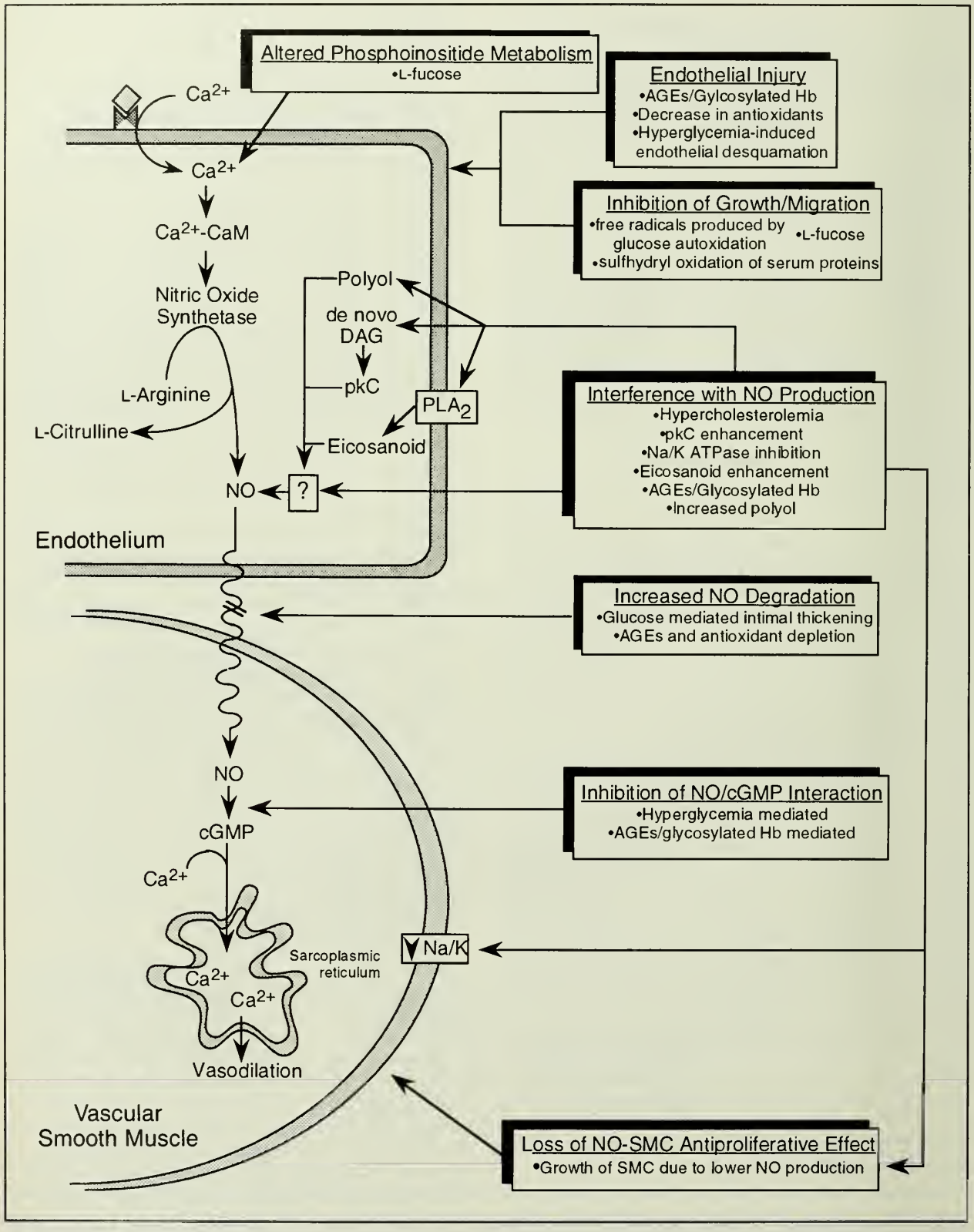

Figure 2.—A multifactorial model of nitric oxide (NO)-mediated vasodilation deficiency in insulin-dependent diabetes mellitus is shown. Various sites of alteration and reported causes of these alterations are illustrated. AGEs = advanced glycosylation end products, ATPase = adenosine triphosphatase, Ca^{2+} = calcium ion, CaM = calmodulin, cGMP = cyclic guanosine monophosphate, DAG = diacylglycerol, Hb = hemoglobin, Na/K = sodium-potassium pump, pkC = protein kinase C, PLA_2 = phospholipase A_2, SMC = smooth muscle cell

Experiments with arginine analogues, which act to inhibit nitric oxide production, are also useful in exploring the contribution of impaired nitric oxide production in IDDM-related vascular complications. In one study, administering *N*-ω-nitro-L-arginine methyl ester caused hypertension in controls and, to a lesser extent, in rats with streptozocin-induced diabetes.[29] Further, several studies show that the capacity of arginine analogues to reduce blood flow is reduced in persons with diabetes.[30-32] These data may be interpreted as evidence for lower basal production of nitric oxide in the endothelial cells of diabetic patients.

Other studies suggest that alterations in endothelial membrane components are caused by hyperglycemic conditions. In one report, investigators using rabbit aorta showed that the activation of protein kinase C through a hyperglycemia-mediated increase in de novo synthesis of diacylglycerol may interfere with endothelial-mediated relaxation by increasing vasoconstrictor prostanoid generation.[33] Even though the increased prostanoid release may directly affect vascular smooth muscle, the same prostanoids through the formation of oxygen radicals may also inhibit the activity of EDRF before it reaches smooth muscle,[34] thus compounding the impairment in relaxation. It has also been suggested that increased polyol pathway activity (often associated with diabetes, hyperglycemia, or both) contributes to the impairment in endothelial-dependent relaxation. Inhibited acetylcholine-mediated relaxation has been shown in aorta subsequent to increased polyol activity in galactosemic rats and diabetic rabbits, respectively.[35,36] The abnormalities in relaxation were prevented by the administration of an aldose reductase inhibitor that prevents the increase in polyol activity. The authors concluded that an abnormality in nitric oxide metabolism brought about by the increased polyol activity causes the impaired vasodilation.[35]

Although hyperglycemia may be a key factor in the alteration of nitric oxide metabolism, a critical study has shown nonspecific impairment in endothelium-dependent relaxation before serum glucose level elevation in genetically diabetic rats.[37] This suggests that the endothelium may play a primary role in the pathogenesis of vascular disease. Hyperglycemia-mediated alterations in nitric oxide metabolism may occur due to or in parallel to this defect.

Another line of research is exemplified in a study that demonstrated that EDRF release is actually increased from endothelial cells incubated in hyperglycemic media.[38] The authors proposed that this increase in nitric oxide release may be responsible for the pathologic vasodilation sometimes seen in the early stages of uncomplicated diabetes mellitus. Supporting this hypothesis is a study that suggests that inhibiting the inducible isoform of nitric oxide synthase in diabetic rats may help reduce pathologic vasodilation and increased vascular permeability at sites of diabetic complications.[39]

Changes in Nitric Oxide Diffusion

Because of its relatively short half-life,[1] nitric oxide is particularly vulnerable to factors that interfere with its migration from endothelium into the vascular smooth muscle cell. Hyperglycemia-mediated intimal thickening found in blood vessels from diabetic subjects may increase the diffusion time. It was reported that hyperglycemia increased the expression of the fibronectin gene in diabetes, which results in intimal thickening.[40] This alteration is not readily reversible. Another study showed increased synthesis of basement membrane components in endothelial cells cultured in hyperglycemic conditions.[41]

An increased amount of advanced glycosylation end products and depleted numbers of antioxidants are associated with an increase in nitric oxide degradation at the endothelial cell smooth muscle junction. One study showed that advanced glycosylation end products accumulate on basement membrane collagen and chemically inactivate nitric oxide.[42] Other studies demonstrated that advanced glycosylation end products quench nitric oxide in vivo and in vitro and that their inhibition with amino guanidine prevents nitric oxide quenching and restores endothelium-dependent relaxation in experimental models of diabetes.[43]

Changes in Cyclic Guanosine Monophosphate-Vascular Smooth Muscle Metabolism

Several studies have documented hyperglycemia-induced changes in smooth muscle responses to agonist-mediated vasodilation and to exogenous sources of nitric oxide that affect nitric oxide-guanylate cyclase coupling, cyclic-GMP generation, or both. In one, cyclic-GMP levels were shown to be reduced in pig aortic endothelial cell monolayers exposed to hyperglycemic conditions.[44] In an experimental paradigm that looked at rats with streptozocin-induced diabetes, an impairment in nitric oxide-dependent cyclic-GMP generation was found in the glomeruli of the diabetic animals.[45] Although the lower cyclic-GMP levels reported in these preparations may be the direct result of lower nitric oxide production, a study suggests that there can be a primary deficiency in the cyclic GMP of smooth muscle cells.[46] The investigators showed that low concentrations of glycosylated hemoglobin inhibited acetylcholine-induced and exogenous nitric oxide-induced relaxation in rat aorta,[46] suggesting that the cyclic-GMP activity is altered in this experimental model of diabetes. The lower levels of cyclic GMP generated in diabetic subjects would lead to reduced Ca^{2+} sequestration and hence an impaired vasodilation.

Hyperglycemic conditions have also been shown to affect the vascular sodium-potassium ATPase. It was shown that hyperglycemia-mediated inhibition of the vascular sodium-potassium ATPase in the rabbit aorta is mediated through endothelium-derived nitric oxide.[47] This inhibition of sodium-potassium ATPase was similarly evoked by exposure to an arginine analogue, L-nitromonomethyl arginine, in normal glucose,

confirming that the primary alteration is a decrease in endothelial nitric oxide generation. An inhibited sodium-potassium ATPase in the smooth muscle would be expected to depolarize those cells and antagonize the efficacy of vasodilatory stimuli.

Finally, we must consider the nonspecific effects of lowered basal nitric oxide production on vascular smooth muscle cells. Nitric oxide exerts an antiproliferative effect in the smooth muscle through a cyclic-GMP–mediated process.[48] A loss or decrease of nitric oxide production is therefore associated with hypertrophy and hyperplasia of vascular smooth muscle that is characteristic of vascular disease. This increase in smooth muscle growth and proliferation results in a higher vascular smooth muscle "load" for each endothelial cell. Nitric oxide-mediated vasodilation may be compromised because of lower responsiveness of the smooth muscle cells. Consistent with this hypothesis, it was reported that advanced glycosylation product-mediated destruction of nitric oxide inactivated the antiproliferative influence of nitric oxide on aortic smooth muscle.[42] These data support the idea that vascular smooth muscle is less sensitive to nitric oxide in patients with diabetes. (See Figure 2 and Table 2 for comprehensive illustration and references.)

Summary and Conclusions

Evidence indicates that many of the vascular complications associated with IDDM may result from alterations in endothelial-derived nitric oxide production and action. Several changes in the metabolism of nitric oxide were considered, as were changes in the structure of endothelial and smooth muscle cells. Factors that compromise nitric oxide diffusion and signal transduction in the smooth muscle cell were also discussed. The alteration in nitric oxide function is an important factor associated with vascular disease in patients with diabetes, and such a deficiency could contribute substantially to the development of vascular complications in diabetes. Persons with diabetes may benefit from therapeutic agents that target nitric oxide pathways, such as nitroglycerin and other nitric oxide-donating compounds. Complications such as increased vascular permeability may not be corrected by nitric oxide supplementation therapy, however. Further investigation should be undertaken to evaluate these compounds in the control or perhaps prevention of the vascular complications that are major factors in the morbidity and mortality of diabetes mellitus.

Other studies not discussed in this article suggest that nitric oxide is also altered in its capacity as a neurotransmitter in diabetes[49] and that it may be responsible for the destruction of pancreatic β-islets in the autoimmune development of IDDM.[50] These observations shed further light on alterations of nitric oxide in not only the course of vascular complications but in the pathogenesis of diabetes itself and warrant further investigation.

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TABLE 2.—*Alterations of Insulin-Dependent Diabetes Mellitus Affecting Endothelium-Derived Relaxation Factor–Mediated Vasodilation*

Alteration	*Reference*
Endothelial injury or desquamation	Popova et al, 1988[13]; Gilcrease and Hoover, 1991[14]
Inhibition of endothelial growth	Curcio and Ceriello, 1992[15]; Nakao-Hayashi et al, 1992[16]; Stefani et al, 1992[21]
Inhibition of endothelial migration	Mascardo, 1988[20]
Change in endothelial phosphoinositide metabolism	Stefani et al, 1992[21]
Change in nitric oxide production	Lash and Bohlen, 1991[22]; Azadzoi and Saenz de Tejada, 1991, 1992[23,24]; Nakamura et al, 1993[25]; Kiff et al, 1991[26]; Haefliger et al, 1992[27]; Pelligrino et al, 1992[28]; Abiru et al, 1993[29]; Taylor et al, 1992[30]; Lawrence and Brain, 1992[31]; Elliott et al, 1993[32]; Tesfamariam et al, 1991, 1993[33,36]; Bohlen and Lash, 1993[34]; Cameron and Cotter, 1993[35]; Miyata et al, 1992[37]
Intimal thickening	Roy et al, 1990[40]; Cagliero et al, 1988[41]
Increased nitric oxide degradation	Hogan et al, 1992[42]; Bucala et al, 1991[43]
Change in cyclic-GMP generation or nitric oxide-guanylate cyclase coupling	Weisbrod et al, 1993[44]; Craven et al, 1994[45]; Rodríguez-Mañas et al, 1993[46]
Smooth muscle hypertrophy or hyperplasia	Hogan et al, 1992[42]

cyclic GMP = cyclic guanosine monophosphate

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Epitomes

Important Advances in Clinical Medicine

Pathology

Yutaka Kikkawa, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under the direction of Yutaka Kikkawa, MD, and the panel.

Cervical Pathology—The Bethesda System and the 'Atypical Squamous Cells of Undetermined Significance' Controversy

THE BETHESDA SYSTEM for reporting cervicovaginal cytologic examinations was first introduced by the National Cancer Institute in 1988, and criteria for using uniform terms and consistently reporting these examinations were published by the Bethesda work group in 1994. Among the many reasons cited for creating this system was the recognition that Papanicolaou's original classification system did not reflect the current understanding of cervical carcinoma. Some laboratories continued to use the Papanicolaou classification system, although there was no consistency in how it was applied, and other laboratories used nomenclature borrowed from surgical pathology or created their own terminology. The Bethesda System, therefore, was designed to provide a uniform diagnostic terminology for reporting cervicovaginal cytologic examinations.

Among the most controversial aspects of the Bethesda System has been the new diagnostic category, "atypical squamous cells of undetermined significance" (ASCUS). Before the publication of system criteria, cytopathologists and technologists were uncertain which cells to place in the ASCUS category, and clinicians were unsure of the importance of this diagnosis and how to treat patients given the diagnosis. It has been recognized that the failure to use strict cytologic criteria to define an abnormal smear can result in enormous variation in the prevalence rate of abnormal Pap smears. Applying strict criteria for diagnosing ASCUS has been found to increase the cytologic detection of clinically important lesions from 25% to 61.3%.

The Bethesda work group recognizes that individual pathologists may use the ASCUS diagnosis differently. The newly published criteria emphasize, however, that ASCUS is not synonymous with previously used terms such as "atypia," "benign atypia," "inflammatory atypia," or "reactive atypia." These other terms referred to lesions currently classified by the system as "reactive cellular changes." An ASCUS diagnosis is meant to convey the differential diagnostic problem between a benign reaction to a stimulus versus a low-grade squamous intraepithelial lesion. It appears that some consistency in the application of ASCUS is being achieved. The College of American Pathologists' Interlaboratory Comparison Program in Cervicovaginal Cytology (PAP) survey indicates that by December 1993, 82.5% of the 903 participating laboratories limited the use of "atypia" terms to abnormalities of undetermined importance.

Acceptable rates for ASCUS diagnoses are currently being defined. Clinicians are suspicious of overdiagnosis that may obligate them to provide expensive and time-consuming follow-up evaluations. The Bethesda work group has suggested that the rate of ASCUS diagnoses should not exceed two to three times the rate of squamous intraepithelial lesion diagnoses. The College of American Pathologists' PAP program supports the target value of the ratio of the diagnosis of ASCUS to that of squamous intraepithelial lesion of 2:1 to 3:1 and has found that this ratio is more constant between laboratories than the ASCUS rates because patient groups may vary. Therefore, it has been suggested that the ratio of the ASCUS diagnosis to that of squamous intraepithelial lesion can be used for interlaboratory comparisons and as a monitor over time within laboratories or between individual cytopathologists and technologists. The Quality Assurance Committee of the California Breast and Cervical Cancer Control Program similarly has investigated this ratio to monitor participating laboratories. Their preliminary results indicate that this is a useful means of interlaboratory comparison and that the ASCUS diagnosis is used somewhat consistently.

The College of American Pathologists' 1993 PAP survey indicates that 62% of laboratories will qualify an ASCUS diagnosis as favoring a reactive or premalignant process, and 53% will give a written follow-up recommendation in ASCUS reports in most of these cases.

Interim guidelines for the follow-up of ASCUS Pap smears have recently been published. Future trends in the use of the system should include increased consistency in using the ASCUS diagnosis and a better understanding of the diagnostic problem this term is trying to communicate, so that appropriate follow-up can be instituted.

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Serum Prostate-Specific Antigen Assay—An Update

PROSTATE-SPECIFIC ANTIGEN (PSA) is synthesized in the epithelial cells of the prostate gland and is perhaps the best tumor marker discovered thus far. The tissue specificity of PSA makes it the most useful marker available for the diagnosis and management of prostate cancer. Lack of cancer specificity is its only drawback. Benign conditions, such as benign prostatic hyperplasia, prostatitis, and infarction, can also be associated with elevated serum PSA levels. Because prostate cancer is frequently associated with old age in men and is a major cause of death for men, a test capable of detecting prostate cancer before the lesion extends outside the confines of the prostate gland is in demand.

Clinical Utility

Because of its tissue specificity, the PSA assay is particularly useful for monitoring the success of surgical prostatectomy. Complete removal of the prostate should result in an undetectable PSA level; any measurable PSA after radical prostatectomy would indicate residual prostatic tissue or metastasis. In those cases, increasing PSA concentrations strongly indicate a recurrent disease. If, however, the detectable serum PSA level after radical prostatectomy is caused by incomplete resection of the gland and not persistent disease, the level should remain unchanged on extended follow-up. Because of the specificity of PSA, the ability of the assay to detect residual prostatic tissue or the recurrence of prostate cancer at an early stage cannot be replicated by other tumor markers. It should be noted that the half-life of serum PSA is about 3 to 4 days; therefore, it will take 30 days for a serum PSA at 50 μg per liter (50 ng per ml) to drop to an undetectable range after surgical therapy. Measuring the PSA level within a month after curative radical prostatectomy is not recommended. Also, serum PSA should not be measured during the course of irradiation treatment, as a transient and modest increase of PSA may occur that could be misinterpreted as disease progression.

The tissue specificity of PSA also makes the test an excellent tool for detecting recurrence after radical prostatectomy. There has been a great demand for the development of an ultrasensitive PSA test that would allow recurrence and metastasis to be detected early, thus providing a better opportunity for successful treatment. Many commercial PSA tests now available are capable of detecting serum PSA levels below 0.1 μg per liter.

In general, no tumor markers are recommended for screening. The use of serum PSA levels in combination with either digital rectal examination (DRE) or transrectal ultrasonography of the prostate as a screening tool for detecting clinically important prostate cancer has been recommended by some. Screening may not only prevent the death of about 30,000 to 40,000 active men from prostate cancer each year, but also permit treatment of organ-confined, potentially curable prostate cancer discovered in men with a life expectancy of more than ten years.

Improvements on Assay Use

The PSA test is tissue- but not cancer-specific. There is substantial overlap in serum PSA levels between men with benign prostatic hyperplasia and those with prostate cancer, especially in the range of 4 to 10 μg per liter. Therefore, there is also a need to improve the current PSA test to differentiate between the two disorders. Two interesting and noteworthy new approaches have been developed for improving the specificity and sensitivity of PSA testing: the measurement of PSA density and the determination of the rate of increase in PSA concentration.

One approach has been to divide the serum PSA concentration by the volume of the prostate gland (determined by transrectal ultrasonogram); the result is the PSA density. A mildly elevated serum PSA level associated with a small prostate gland may be indicative of cancer, whereas the same value in a patient with a large gland may be indicative only of benign hyperplasia. It was recommended that if the findings of the DRE are normal and the serum PSA level is between 4 and 10 μg per liter (by Hybritech assay), the patient should undergo transrectal ultrasonography to determine the volume of the prostate gland. The mean PSA density has been established as 0.285 for men with positive biopsy results and 0.199 for men with negative biopsy results. The merit of PSA density is to distinguish benign prostatic hyperplasia from prostate cancer for men who have serum PSA levels within the intermediate range (4 to 10 μg per liter) who have had normal findings on a DRE, but it may not detect all organ-confined prostate cancers.

Another approach to improve the specificity of the serum PSA test is to calculate the rate of change of serum PSA levels. This rate appears to be more useful than the actual serum PSA level for detecting and staging prostate cancer. For example, for serum PSA values well within

the reference range (<4 μg per liter), a change from 1.8 to 2.9 μg per liter in a year's time could signal the presence of prostate cancer. If the PSA test selected is reliable over that period of time, this new approach allows for the early detection of cancers at a more curable stage than would have been possible with conventional criteria. It is now recommended that PSA velocity should be determined from three consecutive measurements within a year. A PSA velocity test showing a consistent increase of 0.75 μg per liter per year or greater, based on three consecutive determinations, is suggestive of cancer and warrants further evaluation. Both new approaches point out that PSA concentrations can be in the normal range even in the presence of cancer. Consequently, an accurate and precise determination of PSA levels within the normal concentration range will be required to take advantage of these two new methods.

One area that has not received enough attention is the use of age-adjusted reference values, especially the normal reference range for people at an older age. An age-specific reference range for serum PSA would possibly detect organ-confined prostate cancers earlier in younger men (men with a life expectancy longer than 10 years) at a time when the tumors are possibly more susceptible to cure. Based on the new reference ranges, fewer cancers in older men—who might have clinically insignificant tumors or have a less than ten years' life expectancy and not benefit from surgical treatment—will be detected. In the past, 4 μg per liter was the upper normal cut off for men at all ages. The recommended age-specific serum PSA reference ranges are 0.0 to 2.5 μg per liter for men 40 to 49 years, 0.0 to 3.5 μg per liter for men 50 to 59 years, 0.0 to 4.5 μg per liter for men 60 to 69 years, and 0.0 to 6.5 μg per liter for men 70 to 79 years. Studies have indicated that the new age-specific serum PSA reference ranges appear to make PSA a more sensitive tumor marker for men younger than 60 years and a more specific tumor marker for men older than 60 years.

Prostate-Specific Antigen Composition in Serum

Prostate-specific antigen has recently been found to be a serine protease capable of complexing with various protease inhibitors. Consequently, PSA is not free in the blood circulation, but exists largely as PSA complexes with protease inhibitors. The major form of PSA complexes found in the serum is PSA–α_1-antichymotrypsin. The ratio between PSA–α_1-antichymotrypsin and free PSA in the serum is not constant; the ratio increases with increasing concentrations of total PSA. Most important is the finding that the percentage of PSA–α_1-antichymotrypsin complex of the total serum PSA is higher in patients with prostatic cancer than in those with benign prostatic hyperplasia. Therefore, the PSA–α_1-antichymotrypsin value has a higher sensitivity for cancer than the assay for total PSA. In other words, the free serum levels of PSA are substantially lower in patients with untreated prostate cancer than in those with benign hyperplasia; the free serum PSA concentration does not correlate with the total serum PSA or PSA–α_1-antichymotrypsin.

Unfortunately, all current PSA kits were designed to measure free PSA in the serum. Also, PSA values produced by different commercial kits are not always compatible. There are two major reasons for these discrepancies: antibodies used in various commercial PSA kits do not have the same specificities for both free PSA and PSA–α_1-antichymotrypsin complex in the serum, and the calibrators used in various kits not only are not identical to each other, but also do not match the PSA composition found in patients' serum. It was suggested from many studies that the lack of a uniform calibrator among various commercial kits largely accounts for the different PSA values produced by different kits on the same specimens.

New-Generation Assay

A logical improvement for the current PSA kits is to change the focus from the measurement of total PSA to that of PSA–α_1-antichymotrypsin complex, because there is an excellent correlation between serum concentrations of PSA–α_1-antichymotrypsin and total PSA in random and in serial specimens. Therefore, using an assay that specifically measures the PSA–α_1-antichymotrypsin complex in the serum not only simplifies the preparation of a calibrator, but eliminates the difficulty of antibody selection. The new-generation assay, which will be available soon, will also improve the test's specificity for prostate cancer.

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Specimen Quality and Accuracy of Fine-Needle Aspiration Biopsies

OVER THE PAST 20 years, fine-needle aspiration biopsy (FNAB) has become an increasingly popular tool in the United States for diagnosing palpable and—with the adjunctive use of computed tomography (CT) or ultrasonography—deep-seated lesions arising in many body sites.

The accuracy of fine-needle aspiration as an effective diagnostic tool has varied greatly in recent reports: the sensitivity of FNAB to detect malignant neoplasms has ranged from 65% to 98% and the specificity (the ability to rule out malignant neoplasms unequivocally) from 34% to 100%. Looking at these results, the questions are why there is such a vast discrepancy and whether the test has use. In well-trained, experienced hands, however, FNAB is an accurate, cost-effective, and well-tolerated diagnostic procedure.

The principle of FNAB is simple, but its appearance is deceiving, leading to many practitioners doing FNABs without proper training or enough practice to maintain effective skills. Three components are necessary to obtain an accurate diagnosis: adequate specimen sampling, proper specimen preparation, and accurate microscopic interpretation. It is generally well recognized that special skill is required to interpret these specimens, but the importance of specimen quality is less well known, especially among clinicians. In analyzing the literature, it is clear that whereas mistakes at the microscope are the culprits in some inaccurate diagnoses, suboptimal lesional sampling and preparation are responsible for the majority.

In recent years, the increased interest in FNAB among pathologists has led to a growing number of residency training programs that include training in cytologic examination of fine-needle aspirations. A growing number of postgraduate education programs are being offered, and several institutions are offering fellowships in cytopathology. All of this has increased the level of experience in the community.

A good way to institute proper FNAB "basic training" is to teach the basic sampling and smearing techniques on bench material, such as animal liver or excised tumor tissue. Two supervised sessions, with time for practice in between, should prepare trainees for doing supervised FNABs in clinical situations. At least 100 to 200 cases within a six-month period are necessary to achieve an acceptable level of proficiency with the procedure, enabling a practitioner to produce diagnostic material in more than 95% of cases. All cases should be reviewed microscopically by the operator, and at least 25% of the procedures should be supervised, especially difficult cases. To maintain this level of skill, the operator should then do at least 20 biopsies per month.

In this manner, adequate tissue sampling techniques can be used, rendering FNAB a highly accurate, cost-effective method of diagnosis. When integrated into the "triple diagnosis for breast disease," for example, FNAB findings are considered along with mammographic findings and the clinical impression. If the FNAB reveals significant atypia and the clinical impression or mammogram indicates possible cancer, the patient is referred for open biopsy; all other patients are observed clinically. This method reduces morbidity, enhances turnaround time, and the per-case savings is about $700 or, for all breast cancer patients in the United States, a savings of close to $400 million, with a false-negative rate of about 1%.

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Molecular Pathology and Cancer Genetic Screening

WITH THE RECENT, highly publicized discovery of the gene *BRCA1* and its relationship to the familial susceptibility to breast and ovarian cancer, the field of diagnostic molecular pathology has moved into the public consciousness. Along with other important discoveries, such as the genes related to hereditary polyposis and nonpolyposis colon cancer, gene mutations in multiple endocrine neoplasia type II (MEN II), and the linkage of a tumor-suppressor gene (*p53*) to many cancers, molecular oncology is emerging as a vital area in the diagnosis and clinical treatment of neoplasia. These discoveries have brought excitement, but also, with closer scrutiny, trepidation.

Cancer, with its specific chromosomal and nucleotide aberrations, is now being viewed as a true genetic disease. The simplistic hope that a single mutation causes a defined disease has, however, been replaced by the realization that inherited diseases carry mutations unique to themselves. In diseases such as familial breast cancer, familial colon cancer, and MEN II, there are a myriad of mutations. In only a few circumstances does a predominant mutation evolve that lends itself readily to standard molecular diagnostic testing.

Multiple endocrine neoplasia type IIA (MEN IIA), an autosomal dominant and nearly fully penetrant hereditary cancer syndrome, leads to the development of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia. The gene causing MEN IIA, the *RET* proto-oncogene on chromosome 10, functions as a receptor tyrosine kinase. Mutations in the *RET* proto-oncogene are all point mutations; 93% occur in two hot-spot regions in the gene. By using the polymerase chain reaction (PCR), an efficient and inexpensive tool, defined regions of the *RET* proto-oncogene containing the hot-spot regions can be amplified. Mutations change the DNA sequence and create or abolish restriction endonuclease cleavage sites. If restriction endonucleases are judiciously chosen, the PCR product can be digested and the fragments can be size-fractionated. These digest patterns can distinguish affected persons. In fact, each specific mutation can be identified with this technology. Laboratories often begin screening for possible MEN IIA mutations by examining the two hot spots; through these screens, 93% of all disease carriers can be identified. If this search yields a normal pattern, a more stringent analysis is begun by using the same technology at less frequently mutated regions of the gene. As many as 95% of all disease carriers can be detected by this approach. Once a mutation is identified in a family, other members of the kindred can then be screened with 100% sensitivity. With early diagnosis, affected persons can be treated

aggressively and identified unaffected persons can be spared annual invasive and expensive clinical screening.

The prospect of a molecular diagnostic test for familial breast cancer was thought to be imminent with the cloning of the *BRCA1* gene. Unfortunately, the evidence thus far indicates that the quest for a comprehensive yet economically feasible DNA test for at-risk persons is formidable. The first difficulty stems from the indication that mutations in *BRCA1*, most likely a tumor-repressor gene, are extremely heterogeneous, with most of those identified so far unique to each family. With no predominant mutation(s) to screen for, each of the 22 exons in the *BRCA1* gene must be sequenced and analyzed. This will be enormously expensive and time-consuming. Second, *BRCA1*, although dominantly inherited, is not fully penetrant. Each of the five affected families initially studied had at least one female member older than 80 years positive for a *BRCA1* mutation but with no detectable breast cancer. Thus, mutations in *BRCA1* do not indicate a 100% probability of breast cancer developing, and their presence may not necessitate prophylactic mastectomy. Third, familial breast cancer is estimated to account for only 10% of all cases of breast cancer. The *BRCA1* gene is predicted to occur in 45% of cases of familial breast cancer; a second gene, *BRCA2*, apparently occurs in a similar proportion. A normal, nonmutated *BRCA1* gene does not indicate freedom from disease; a woman may get breast cancer related to *BRCA2*, or some other gene, and she is still susceptible to sporadic breast cancer. For all these reasons, molecular diagnostic screening for breast cancer predisposition presents extraordinary technical challenges; the results obtained raise clinical and ethical dilemmas.

Molecular diagnostic testing is now in its infancy with regard to two colorectal cancer syndromes. The first, familial adenomatous polyposis, is an autosomal, dominantly inherited, colorectal cancer syndrome with the hallmark of multiple adenomatous polyps (>100) that progress into cancer. The gene, adenomatous polyposis coli (*APC*), has been mapped to chromosome 5q21. Most kindreds have unique mutations in the *APC* gene, but two mutations occur in about 30% of cases. Molecular screening at this time involves linkage studies by DNA polymorphisms and direct sequencing of the gene. The second colorectal cancer syndrome, hereditary nonpolyposis colorectal cancer, is an autosomal dominant disorder that accounts for 4% to 6% of all colorectal cancers. The primary responsible genes (mismatch repair genes) are located on chromosome 2 (*HMSH2*) and chromosome 3 (*HMLH1*), but there are apparently others as well. Currently, linkage studies are the only feasible approach in most families, although functional protein-based assays are being developed.

Each week the literature is peppered with reports about the *p53* tumor-repressor gene. It is responsible for programmed cell death and cell-cycle arrest, and it has been linked to cancers of the bladder, breasts, lungs, colon, brain, and other tissues. Although germline *p53* mutations have been linked to a small number of familial cancers (such as the Li-Fraumeni syndrome), somatic mutations can be found in sporadic tumors where they may aid in disease prognosis. For example, it was shown recently that tumors lacking wild-type *p53* were resistant to anticancer agents. Currently both DNA-based and immunohistochemical techniques can be used to detect mutated *p53*.

Diagnostic molecular oncology is evolving at a rapid pace, driven by the explosion of knowledge about the molecular biology of cancer and the frenzied cloning of disease genes under the impetus of the human genome project. But as new DNA tests emerge, diagnostic and ethical guidelines need to be developed and adhered to, despite the economic incentives and public appetite for this rapidly expanding field of pathology.

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Predisposition to Thrombosis by a Factor V Mutation Causing Hereditary Resistance to Activated Protein C

THROMBOEMBOLIC DISEASES resulting from the inappropriate activation of the blood coagulation cascade represent a major cause of morbidity and mortality worldwide, affecting about 1 in 1,000 people per year. The most common of these syndromes are deep venous thrombosis and its direct sequela, pulmonary embolism. Although specific risk factors for venous thrombosis have been well characterized (prolonged immobility, estrogens, major operations, trauma), genetic factors play a pathogenic role in at least a third of cases. Inherited mutations within the genes for the anticoagulant proteins antithrombin III, protein C, and protein S together account for only 5% to 10% of these thrombosis-prone families. A much larger number of these families have recently been found to have hereditary resistance to activated protein C, resulting from a highly prevalent missense mutation within the gene for coagulation factor V. The laboratory detection of this resistance to activated protein C is of clinical utility, as affected persons represent an important proportion of those with sporadic or recurrent thrombosis who may then benefit from prophylactic anticoagulant therapy.

Because activated protein C normally inhibits fibrin formation by cleaving and inactivating coagulation factors Va and VIIIa, the addition of activated protein C to normal plasma substantially prolongs the clotting time. In

contrast, the addition of activated protein C to the plasma from patients with hereditary resistance to activated protein C does not adequately prolong the clotting time. The functional laboratory test for this disorder is therefore an "activated protein C resistance ratio," a ratio between two activated partial thromboplastin times (aPTTs), one with the addition of activated protein C and one without. Activated protein C resistance ratio testing on families with histories of thrombophilia has shown that this phenotype is inherited as an autosomal dominant trait.

The genetic basis for hereditary resistance to activated protein C has recently been defined as a single point mutation in coagulation factor V at the site where activated protein C normally cleaves and inactivates the factor Va procoagulant. One or both copies of the factor V gene from patients with resistance to activated protein C thus carry a single G to A missense mutation converting arginine 506 to glutamine. After activation, this mutated factor Va cannot be efficiently cleaved by activated protein C; its procoagulant activity therefore persists, and the risk of thrombosis subsequently increases. The increased thrombotic risk associated with the heterozygous factor V mutation appears to be about five to ten times that of the normal population. The risk for patients carrying a homozygous factor V mutation is substantially greater.

The codon 506 factor V mutation is by far the most common genetic risk factor for venous thrombosis. About 20% of patients with a first episode of deep venous thrombosis and 60% of patients with recurrent or pregnancy-associated thromboembolism have functional resistance to activated protein C; the vast majority of these defects result from the codon 506 factor V mutation. This mutation is also prevalent in normal persons with heterozygote frequencies of 2% to 8% in different populations that have been screened. Of 197 randomly selected Red Cross blood donors in Portland, Oregon, for example, 15 (7.6%) were heterozygous for the codon 506 factor V mutation. The absence of disease in most of those carrying this mutation implies that, for most people, the formation of symptomatic thrombosis requires additional factors over and above this single defect. A two-hit hypothesis for thrombosis might explain some of these observations; patients with heterozygous resistance to activated protein C may then suffer thrombotic episodes only when additional thrombotic risks (genetic, physical, or biochemical) exist simultaneously. Examples of conditions likely to be synergistic with this disorder for symptomatic thrombosis include a second copy of the mutated factor V allele (that is, homozygosity), protein C or S deficiency, antithrombin III deficiency, the presence of a lupus anticoagulant, and homocystinemia. In support of this two-hit hypothesis, it has recently been shown that of heterozygous persons with activated protein C resistance, more than 70% with a simultaneous factor V mutation suffered a thrombotic event compared with only 30% of those without this second deficit.

Laboratory tests for the diagnosis of activated protein C resistance include the functional activated protein C resistance ratio test and the direct DNA-based detection of the factor V codon 506 mutation. The presence of this mutation can be directly determined by the isolation of DNA from peripheral blood leukocytes, PCR amplification with primers flanking the factor V mutation site, and digestion of the PCR product with the restriction enzyme *Mn*II. As the mutation destroys one of the *Mn*II sites within this amplicon, the mutant and wild-type alleles can be easily distinguished on a size-separating gel. In our laboratory, the correlation between the functional and DNA-based tests has been excellent. Anticoagulated patients cannot, unfortunately, be evaluated by the activated protein C resistance ratio test (a modified aPTT); the DNA-based test is then the only diagnostic alternative for this group. Additional clinical indications for the DNA-based (rather than the functional) test for hereditary resistance to activated protein C include patients with lupus anticoagulants, those with borderline activated protein C resistance ratios, the evaluation of homozygotes versus heterozygotes, and the confirmation of genotype in affected persons and their family members.

The accurate laboratory identification of hereditary resistance to activated protein C is of real clinical relevance because some, but not all, of these patients may benefit from long-term anticoagulant therapy. In particular, those heterozygous patients with several previous thrombotic episodes, those with a known genetic "second hit" (including homozygotes), and some with a single "spontaneous" episode of deep venous thrombosis (no known environmental risk) should probably be treated with long-term anticoagulants. In contrast, most heterozygous persons with either no history of thrombosis or with a single, previous episode of deep venous thrombosis induced environmentally (surgery, trauma, or prolonged immobility) should not always be prophylactically treated. Instead, these patients should be thoroughly advised of the signs and symptoms of deep venous thrombosis or pulmonary embolism, encouraged to seek early medical attention for their suspected occurrence, and given optimal antithrombotic prophylaxis for surgical therapy, pregnancy, and prolonged immobility. Until definitive clinical studies on these patient groups are published, these therapeutic recommendations are based on the fact that in the great majority of persons heterozygous for activated protein C resistance, thrombosis does not develop until additional "secondary" events occur.

Because this highly prevalent genetic mutation was identified only recently, the full spectrum of its clinical manifestations remains unknown. Does the highly prevalent factor V mutation, for example, contribute to the arterial thrombotic episodes that cause myocardial infarction and cerebrovascular disease? The absence of an increased frequency of heterozygotes in a population of elderly stroke patients suggests that this mutation may not predispose to common arterial thrombotic events. Alternatively, should laboratory screening for hereditary resistance to activated protein C be instituted in thrombosis-prone populations (pregnant women, patients with atrial fibrillation, and before major orthopedic operations) to identify those who might benefit from prophylactic an-

ticoagulants? The answers to these and other pertinent clinical questions may allow us to direct antithrombotic therapy at those most likely to have thrombosis and, perhaps more important, to avoid it in others.

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Microalbuminuria

THE DEVELOPMENT of clinically serious nephropathy is a common complication of diabetes mellitus. At least 30% of new patients with end-stage renal disease have diabetic nephropathy. Among these cases, half have insulin-dependent diabetes mellitus (IDDM) and half have non–insulin-dependent diabetes (NIDDM).

The urinary albumin excretion in normal young subjects is less than 10 μg per minute (about 15 mg per day), but it increases slowly with age. Overt or clinically detectable proteinuria is commonly defined as a urinary albumin excretion rate greater than 200 μg per minute (about 300 mg per day). Thus, there exists an intermediate range of 20 to 200 μg per minute (30 to 300 mg per day) that is definitely not normal and is associated with major clinical findings. This persistent increase in subclinical urinary albumin excretion has been called "microalbuminuria." Hence, the term does not imply excretion of a variant of albumin but of smaller quantities than those detectable by traditional dipstick methods.

Microalbuminuria is strongly associated with the eventual development of nephropathy in 80% of patients with IDDM and 25% of patients with NIDDM. It is also associated with increased morbidity and mortality. Those IDDM patients with microalbuminuria who were treated for hypertension had substantial decreases in the urinary albumin excretion rate and a pronounced decrease in the rate of decline of renal function. Thus, microalbuminuria is an early marker for the development of diabetic nephropathy and possibly for increased mortality as well. The determination of this condition in patients who are "dipstick-negative" could be clinically important. It has been recommended that microalbuminuria be determined annually in patients with IDDM of more than five years' duration and in all patients with NIDDM. The detection of notable microalbuminuria in these patients may warrant altered treatment, even if other variables (such as blood glucose or glycated hemoglobin levels) are not substantially abnormal.

Although the primary indication for monitoring microalbuminuria is to evaluate the renal status in diabetes mellitus, recent studies suggest that such measurement may also be helpful in patients with preeclampsia, drug nephrotoxicity, and severe hypertension.

Traditional urine dipstick methods are not sufficiently sensitive to detect mild to even moderate microalbuminuria. More than a quarter of patients with IDDM and a third of those with NIDDM who were negative for albumin by dipstick were found to have clinically substantial microalbuminuria.

A variety of sensitive quantitative methods are available for monitoring microalbuminuria. These include radioimmunoassay, enzyme-linked immunosorbent assay, and nephelometric immunoassays. The clinical chemistry laboratory at our medical center (University of California, San Diego) uses a rate nephelometric assay. The method detects as little as 2 μg per ml of albumin. The preferred specimen is a 24-hour urine collection because this permits the rate of albumin excretion over a protracted period of time to be calculated. Because collecting a 24-hour specimen is not always feasible, timed, short-term collections may be used. Randomly collected specimens should be avoided because the rate of excretion cannot be calculated. If such specimens must be used, the creatinine concentration should also be measured and the ratio of albumin to creatinine determined. The normal urine albumin:creatinine ratio is less than 0.01. Patients with microalbuminuria generally have values greater than 0.02. In patients with IDDM, there is a strong association between the ratio determined in a 4-hour collection and the 24 hour-urinary albumin excretion rate, with a high positive predictive value. The test costs about $65.

In addition to the importance of timed specimens, urine specimens should not be collected during periods of excessive exercise or prolonged standing. Specimens should not be collected from patients with hematuria or urinary tract infection. Glass containers should not be used because albumin adheres to glass.

Even when these guidelines are observed, day-to-day urinary albumin excretion rates vary considerably. The intraperson coefficient of variation on a daily basis may be as high as 45%. Therefore, it has been suggested that patients have at least three timed urine collections over a six-month period. A patient would be considered to have microalbuminuria if the urinary albumin excretion were increased in two of the three specimens.

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Alerts, Notices, and Case Reports

'Crystal' and Pregnancy Methamphetamine-Associated Maternal Deaths

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ALTHOUGH COCAINE AND OPIATES have attracted greater interest in the literature and in the popular press, amphetamines are abused by pregnant women in California with nearly the same frequency as cocaine; among white women, abuse of amphetamine is more common than that of cocaine.[1]

In a recently published statewide study of the prevalence of drug abuse,[1] 29,494 women had toxicologic screens done during labor. The most commonly detected illicit drugs were cannabinoids (1.88% of patients), cocaine (1.11%), and amphetamines (0.66%). Among the 10,615 white, non-Hispanic patients tested, 1.32% had a positive screen for amphetamines, with 0.60% testing positive for cocaine. In this study, the rates were 20-fold higher for both amphetamine and cocaine abuse among smokers than among nonsmokers and more than 10-fold higher among patients not receiving prenatal care than among those having prenatal care.

Amphetamines have been reported to be the most common drugs of abuse in nonpregnant patients in San Diego County and among pregnant women delivering at the University of California, San Diego (UCSD).[2,3] Our experience in the private hospital setting is similar to that at UCSD and reported statewide—among white, non-Hispanic patients, amphetamines appear to be the drug of choice for abuse during pregnancy.

In our obstetric patients, virtually all toxicologic screens positive for amphetamines also show methamphetamines, and patients who admit using amphetamines say that they are using "crystal" or "ice," a highly purified crystalline form of methamphetamine. We report the details of two cases of maternal deaths associated with the abuse of methamphetamine and discuss the myriad of possible adverse effects of crystal use during pregnancy.

Report of Cases

Case 1

The patient, a 26-year-old multipara, was admitted in labor with severe abdominal pain at 37 weeks' gestation. During the pregnancy, the patient had missed numerous prenatal visits and admitted using marijuana, crystal, and occasionally alcohol. The prenatal course had been remarkable only for poor weight gain. The patient had no underlying medical problems.

At the time of admission, the patient had severe and constant contractions. The blood pressure was 120/80 mm of mercury, and the pulse rate was 110 beats per minute. The fetus could not be adequately monitored because of maternal discomfort. The cervix was dilated 4 cm and 80% effaced. Membranes ruptured shortly after admission; thick meconium was present.

Eight minutes after admission, the patient became cyanotic and unresponsive, with gasping respirations. Within two minutes, she had a cardiorespiratory arrest. Electromechanical dissociation was present. Resuscitation included intubation, ventilation, chest compressions, the administration of fluids, inotropic agents, and pressors, and transthoracic pacing. These efforts were unsuccessful. Fifteen minutes after the initiation of cardiopulmonary resuscitation, a cesarean section was done. The infant weighed 2,740 grams and had Apgar scores of 0, 0, 3, 3, and 4 at 1, 5, 10, 15, and 20 minutes, respectively.

Resuscitative efforts for the patient were discontinued after 30 minutes. An autopsy showed amniotic fluid debris in the pulmonary vasculature. The serum methamphetamine concentration measured from a postmortem specimen was 1.8 mg per ml, and the amphetamine level was 0.3 μg per ml. The medical examiner judged the cause of death to be amniotic fluid embolism due to methamphetamine abuse.

The newborn had a stormy course in the intensive care unit, with hypotonia and seizures. He was discharged home on day 31 to the patient's family.

Case 2

The patient, a 25-year-old multipara, was brought to the hospital by ambulance at 37 weeks' gestation with a history of obtundation and seizures for three hours.

The patient had had a single prenatal visit and had planned to give the baby up for adoption. She had no known medical problems. She was normotensive in the physician's office two weeks before being admitted to the hospital.

At admission, her blood pressure was 150/96 mm of mercury, and the pulse rate was 108 beats per minute. Her pupils were 3 mm and fixed, with no corneal reflexes. The patient was unresponsive to any but deep pain and showed decerebrate posturing. Within minutes of arrival, her membranes ruptured and a 2,480-gram male infant with Apgar scores of 8 and 9 was rapidly delivered. The placenta showed a large, fresh area of abruption.

After intravenous access had been established, the patient was given magnesium sulfate, an endotracheal tube was introduced, and she was ventilated. An emer-

(Catanzarite VA, Stein DA: 'Crystal' and pregnancy—Methamphetamine-associated maternal deaths. West J Med 1995; 162: 454-457)

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
HELLP [syndrome] = *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count
UCSD = University of California, San Diego

gency computed tomographic (CT) scan (Figure 1) showed a large intracranial hemorrhage originating in the basal ganglia, tracking in a subependymal location, and breaking into the ventricular system. Cerebral edema was present. Laboratory studies revealed trace protein on a dipstick urinalysis, a hematocrit of 0.36 (36%), a platelet count of 26×10^9 per liter (26,000 per mm^3), and the following serum levels: aspartate aminotransferase, 2,100 units per liter; alanine aminotransferase, 750 units per liter; lactate dehydrogenase, 3,100 units per liter; creatinine, 100 μmol per liter (1.1 mg per dl); and bilirubin, 34 μmol per liter (2.0 mg per dl). The initial diagnosis was eclampsia, the HELLP syndrome [*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count], and intracranial hemorrhage.

The patient was transfused with platelets and treated with phenytoin (Dilantin) as prophylaxis against further seizures. The blood pressure stabilized at 130/80 mm of mercury, and no antihypertensive treatment was required. Despite receiving mannitol, the patient was unresponsive. An intracranial pressure monitor was placed. Treatment included therapeutic hyperventilation and the administration of dexamethasone sodium phosphate (Decadron) and more mannitol, but the intracranial pressure could not be controlled and rose above the mean arterial pressure. A follow-up CT scan showed virtual obliteration of the ventricles. An electroencephalogram showed bilateral epileptiform activity and severe diffuse nonspecific abnormalities. After extensive discussion with the family, support was discontinued on day 8.

A urine specimen obtained at the time of admission showed amphetamines and methamphetamines. The father of the baby, who had initially denied any drug use, admitted that he, the patient, and several friends had smoked crystal and marijuana on the night and early morning before the woman's admission to the hospital.

Autopsy examination established the immediate cause of death as intracerebral hemorrhage originating in the left basal ganglia with extension into both lateral ventricles, cerebral edema, and tonsillar herniation. The underlying causes were judged by the medical examiner to be methamphetamine abuse and preeclampsia.

The infant did well. He had the mild transient hypoglycemia and tachypnea of newborns. A sonogram of his brain was normal. The adoptive parents were fully apprised of the situation, and the infant was discharged home to them on day 6.

Discussion

Methamphetamine is a potent, inexpensive, long-acting psychoactive drug. A highly purified form, crystalline methamphetamine ("crystal," "ice," "crank") is easily synthesized. Unlike its predecessor, "speed," which could be ingested or injected, crystal can be smoked or inhaled and is said to produce an extraordinarily long-lasting euphoric state. Methamphetamine in any form has various dangerous and possibly lethal side effects.[4,5]

Figure 1.—A computed tomographic scan of the brain shows an acute left basal ganglia hemorrhage and a massive amount of intraventricular blood.

Methamphetamine drives the release of catecholamines and dopamine from the presynaptic nerve ending and inhibits presynaptic uptake and degradation of these substances.[5] In addition, methamphetamine depletes catecholamine reserves in the presynaptic terminal. Pharmacologic effects include both α- and β-adrenergic stimulation, including increased blood pressure, pulse rate, cardiac output, and systemic vascular resistance. The immediate toxic effects may include severe hypertension and hypertensive crisis, cerebrovascular accident due to vasospasm, intracranial hemorrhage, cardiac arrhythmias, pulmonary edema, agitation, confusion, seizures, hyperpyrexia, and cardiovascular collapse. Long-term effects may include anorexia, weight loss, aggressive behavior, amphetamine-induced psychosis, and cerebral arteritis.[5,6]

Epidemiologic studies have identified clear risk factors for methamphetamine abuse during pregnancy.[1,3] These risk factors include white, non-Hispanic ethnic background, cigarette smoking, and little or no prenatal

care. The long-term use of methamphetamines may affect personality and judgment[6]; many patients fit the profile described by Dixon: "These are angry, aggressive, difficult parents who have strong denial mechanisms."[3(p440)] In our experience, methamphetamine users rarely identify their substance abuse as a problem, deny use when it is detected by toxicology screens, and may threaten to or actually discontinue prenatal care if the issue is brought up by health care professionals.

Even a highly motivated patient may be unable to quit using crystal. A pregnant medical professional we treated recently described her addiction thus:

> I used drugs in my teens—dope, acid, angel dust, and coke [cocaine]. I even used IV heroin. But I could quit, and I did. I hadn't used anything for six years. Then I tried crystal just once. It was better than heroin, better than cocaine, better than anything. . . . Now I can't get it out of my mind. I'm thinking about it all the time. I've been in drug rehab twice before, and I know as soon as I get out [of in-patient drug rehabilitation] this time, I'll be going back to crystal. It's just too strong.

The detection of methamphetamine use, if not elicited from the patient, is accomplished by laboratory assessment, usually urine toxicologic screening. The threshold set by our laboratory is 300 ng per ml of urine for total amphetamines. Confirmation is by means of gas chromatography and mass spectroscopy, with "positive" screens reported at amphetamine concentrations of 100 ng per ml and methamphetamine concentrations of 100 ng per ml. The threshold for detection by gas chromatography is substantially lower, and a patient who used amphetamines, even in large amounts, a day or two before may have a negative urine screen. Blood levels are seldom used, except by forensic pathologists. Deaths have been reported after intravenous or oral administration of methamphetamine, with levels ranging as high as 1.3 μg per ml.[7]

There have been few series reporting outcomes of pregnancy among patients abusing methamphetamines. Adverse perinatal outcomes have been reported in Scandinavian methamphetamine addicts, including increased rates of preterm birth, intrauterine growth retardation, placental abruption, and fetal distress.[8,9] Three major studies have addressed methamphetamine use in pregnancy in US centers. One found associations with prematurity and low birth weight.[10] The other two showed reduced birth weights relative to the normal obstetric population, but reported no other excesses of adverse outcomes.[11,12] The concern has been raised that babies with exposure to either methamphetamines or cocaine in utero are at risk for intracranial lesions, including intraventricular hemorrhage.[3,13]

Individual case reports raise additional concerns, particularly regarding maternal risks of amphetamine abuse. Amphetamines have been reported to cause cardiovascular collapse during anesthesia for cesarean section.[14,15] The mechanism presumably involves the depletion of epinephrine and norepinephrine reserves, so that the maternal compensatory response to regional anesthesia may be impaired. Amphetamine use has also reportedly caused seizures mimicking eclampsia.[16] These reports were published before the widespread availability of crystal in this country.[14-16] We are not aware of previous reports of obstetric deaths attributed to methamphetamine abuse.

Did amphetamine abuse actually cause the two deaths reported here? Patient 1 arrived at the hospital with tumultuous labor and thick meconium, factors that are often present in amniotic fluid embolism. It has been argued that amphetamines promote uterine hyperactivity by increasing norepinephrine release.[10] This phenomenon has not been investigated in animal models. Cocaine, however, has been shown in vitro to abruptly increase uterine activity; α-adrenergic stimulation and the inhibition of β-receptors (both of which also occur with amphetamine use) are proposed mechanisms.[17] In our experience, hypertonic uterine activity is common in women using amphetamines. We speculate that, in patient 1, methamphetamine use promoted the hypertonic uterine contractions and was a contributing cause of the amniotic fluid embolism.

Patient 2 had the HELLP syndrome, and a massive intracranial hemorrhage caused her death. Intracranial hemorrhage may occur in preeclampsia or in eclampsia, with or without thrombocytopenia. The most common lesions on radiography and at autopsy are petechial hemorrhages, but large hemorrhages occasionally occur.[18-20] In the older obstetric literature and among women in developing countries, intracranial hemorrhage has been reported to be among the most common causes of death in preeclampsia or eclampsia.[20,21] Among recent series in the United States, however, intracranial hemorrhage rarely caused maternal death. For example, among a total of 499 cases of eclampsia reported in two large institutions, 2 maternal deaths occurred, 1 from cardiac arrest before the patient arrived at the hospital and 1 due to magnesium toxicity.[22,23] Among 499 cases of the HELLP syndrome reported from the University of Arizona and the University of Tennessee at Memphis Medical Centers, there were 7 maternal deaths, none due to intracranial hemorrhage.[24,25] In a ten-year experience at tertiary care referral centers caring for more than 60,000 pregnancies, we have encountered 4 other maternal deaths in cases of preeclampsia or eclampsia, none due to intracranial hemorrhage.

Although the cause of the intracranial hemorrhage in patient 2 could have been preeclampsia or eclampsia, intracranial bleeding is also a common complication of methamphetamine abuse.[26] The location of the hemorrhage is far more characteristic of amphetamine abuse than of preeclampsia or eclampsia. Blood pressure fluxes following the patient's use of crystal likely caused the hemorrhage, or at least contributed to the development of bleeding, and therefore the patient's death.

These two maternal deaths occurred among about 22,000 deliveries at the Mary Birch Hospital for Women at Donald N. Sharp Memorial Community Hospital and the Women's Center at Grossmont Hospital in 1992 and 1993. During the same time, the perinatology group serving the Sharp Hospital system and the San Diego community saw numerous additional serious obstetric complications in pregnant women abusing methamphetamines. Apart from patient 2, we cared for two patients with intracranial hemorrhage during the third trimester of pregnancy; one of the two was "high" on "ice" at admission and was a long-term abuser of crystal methamphetamine. We saw two women with cardiovascular collapse following regional anesthesia for delivery. Both required resuscitation with high doses of pressors for prolonged periods of time, and both proved to be long-term users of crystal methamphetamine. Neither patient had underlying medical problems apart from the drug abuse. We also treated three cases of methamphetamine-induced hypertensive crisis and one patient with a grand mal seizure following crystal methamphetamine abuse during the third trimester of pregnancy.

If the statewide prevalence figure of 0.66% is applicable to our referral base of approximately 25,000 deliveries per year, these obstetric problems occurred among approximately 330 amphetamine users. It should be recognized, of course, that our perinatology group is not asked to consult for all serious problems involving the referral base.

The true rate of methamphetamine-related obstetric complications remains to be elucidated by a prospective population-based study. Our experience, however, suggests that methamphetamine use presents a great danger to pregnant women.

How should this information be integrated into obstetric practice? First, obstetric care providers need to be aware of the prevalence of the problem and of the epidemiologic risk factors for amphetamine abuse during pregnancy. We must be willing to test patients who have high-risk characteristics and to educate them regarding the risks of methamphetamine use. Second, clinicians must have a high index of suspicion for drug abuse in evaluating patients with obstetric complications such as hypertensive crisis, abruption, preterm labor, or maternal intracranial hemorrhage. Third, both obstetricians and anesthesiologists need to be aware of the possible interactions of routine medications, such as terbutaline sulfate for hypertonic contractions or preterm labor and regional anesthesia for labor in amphetamine users.

Unfortunately, women who are at highest risk to use crystal often do not seek prenatal care, patients who are identified during their prenatal care as using this drug may withdraw from care, and even highly motivated patients may be unable to control their desire for this highly potent psychoactive and vasoactive drug.

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Congenital Malaria in a Nonidentical Twin

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MALARIA REMAINS the leading cause of parasitic death in the world, causing 200 to 300 million cases of infection annually. In Africa alone, more than a million persons die of malaria each year; most are children. In the United States, more than 1,000 cases are reported annually, almost exclusively from travelers and immigrants from endemic areas; however, mosquito transmission has been reported in California, most recently in 1990.[1]

In contrast, congenital malaria remains relatively rare with only about 300 cases reported worldwide, although this may represent underreporting. In the United States, 49 cases have been reported since 1950.[2] The occurrence of congenital malaria in twins is even rarer with only 5 previous reports in the world literature.[3-7] We report a case of congenital malaria in the second of nonidentical twins.

Report of a Case

The patient, a 1-month-old Asian-Indian girl, was admitted to the University of California, Davis, Medical Center because for a week she had had fever, pallor, lethargy, and poor oral intake. She was born at another hospital prematurely by cesarean section at 33 weeks' gestation. She was the second of nonidentical twins. Both twins had uneventful perinatal courses and were discharged from the hospital after 11 days.

A week before admission, the patient was noted to be eating less and was vomiting her formula. The formula was changed, but there was no notable improvement when she was seen in follow-up three days later. By this time she was noted to be pale and to have tachycardia for which she was admitted with an impression of neonatal sepsis. A regimen of cefotaxime sodium and ampicillin was started. Her leukocyte count was 9.8×10^9 per liter (9,800 per mm^3), her hemoglobin level was 68 grams per liter (6.8 grams per dl), a hematocrit was 0.18 (18%), and the platelet count was 646×10^9 per liter (646,000 per mm^3). After one day, she was transferred to the University of California, Davis, Medical Center for further management when *Plasmodium vivax* was noted on the peripheral blood smear.

(Balatbat ABN, Jordan GW, Halsted C: Congenital malaria in a nonidentical twin. West J Med 1995; 162:458-459)

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On initial evaluation, the neonate was pale, irritable, weighed 2.46 kg (5.4 lb), and had a temperature of 36.7°C (98°F), a heart rate of 148 beats per minute, and a respiratory rate of 56 per minute. Her sclerae were icteric, and the skin was jaundiced. Her abdomen was full but soft, the liver was palpable 2 cm below the right costal margin, and the spleen was palpable 2 cm below the left costal margin. The findings of the rest of the examination were unremarkable.

Laboratory tests revealed a leukocyte count of 5.8×10^9 per liter (5,800 per mm^3), a hemoglobin level of 54 grams per liter (5.4 grams per dl), a hematocrit of 0.148 (14.8%) and a platelet count of 43×10^9 per liter (43,000 per mm^3). The peripheral blood smear again showed a few intraerythrocytic forms of *P vivax*. Her bilirubin level was 54 μmol per liter (3.2 mg per dl); alkaline phosphatase, 177 units per liter; aspartate aminotransferase, 43 units per liter; and γ-glutamyl transferase, 180 units per liter. The Coombs' test was negative.

She was treated with a regimen of chloroquine phosphate with a loading dose of 10 mg base per kg, followed by three doses of 5 mg per kg given at 6, 24, and 48 hours after the initial dose. She was transfused 35 ml of packed erythrocytes. She responded well, and a repeat blood smear showed no parasites. She was discharged after six days.

The patient's mother was a 21-year-old Indian woman who had moved to the United States 11 months before from Punjab, India. She does not have a history of malaria. During the first trimester of her pregnancy, she had had fever for two weeks, which was treated with an unspecified antibiotic. The rest of the course of her pregnancy was uneventful.

She lived in Yuba City with her husband, three children, and other relatives, none of whom had had malaria. Mosquitos are present in this locality, and the babies had been left near windows that did not have protective screens.

The patient's twin was asymptomatic. A peripheral blood smear showed no parasites; she had a leukocyte count of 11.6×10^9 per liter, a hemoglobin level of 115 grams per liter, and a hematocrit of 0.334 with a platelet count of 393×10^9 per liter.

The mother had a leukocyte count of 12.4×10^9 per liter, a hemoglobin level of 133 grams per liter, a hematocrit of 0.40, and a platelet count of 197×10^9 per liter. Her reticulocyte count was 0.02, and the peripheral blood smear did not reveal any malaria parasites. She was given a 14-day course of primaquine phosphate.

The results of serologic tests done at the Centers for Disease Control and Prevention are shown in Table 1.

Discussion

Congenital malaria is a well-described disorder with an occurrence as low as 0.3% in immune mothers to as high as 10% in nonimmune mothers.[3,8] The rarity of congenital transmission is attributed to the effectiveness of the placenta as a barrier to infected cells and to the pas-

TABLE 1.—*Indirect Fluorescent Antibody Titers to* Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, *and* Plasmodium ovale *Antigens in Serum Specimens From the Case Patient, the Mother, and the Other Twin*

Antibody Titers	*Patient*	*Mother*	*Other Twin*
IgG Titer			
P vivax	1:4,096	1:1,024	1:1,024
P falciparum	1:256	1:64	1:16
P malariae	1:256	ND	ND
P ovale	1:256	1:64	1:16
IgM Titer			
P vivax	1:1,024	1:16	ND
P falciparum	1:256	ND	ND
P malariae	1:64	ND	ND
P ovale	1:256	ND	ND

IgG = immunoglobulin G, IgM = immunoglobulin M, ND = none detected

sive transfer of maternal antibodies.[9] Postulated mechanisms for congenital transmission include maternal transfusion into the fetal circulation either at the time of delivery or during pregnancy, direct penetration through the chorionic villi, or through premature separation of the placenta.[9] Although various studies support each of these postulates,[3] transmission at parturition or during labor is thought to be the most likely mechanism.[2]

Immunoglobulin (Ig) M antibody synthesis can start during gestation, and the patient's high IgM titers represent an immunologic response by the infected twin. Immunoglobulin M antibodies may be present in patients with chronic malaria, and the mother's low titer probably indicates chronic low-grade infection.[10] The substantial titers to the heterologous antigens represent cross-reactivity and are not unusual. The IgG in the second twin is from passive acquisition from the mother.

Although the clinical presentation and serologic test results are consistent with either vector-transmitted or congenital malaria, this patient was most likely infected through perinatal transmission. She had never been in an endemic area, and although the *Anopheles* species vector is known to be present in Yuba City, autochthonous cases have not been reported to occur since 1974.[11]

The patient's fever, anorexia, lethargy, anemia, and splenomegaly are the classic presenting symptoms and signs of neonatal malaria. It takes a minimum of ten days for vector-borne malaria to incubate, and the mean presentation of congenital malaria is 5.5 weeks with a range of 0 to 60 weeks. Fever is invariably present, hepatosplenomegaly and anemia were noted in 84% to 93% of cases in a review,[2] and anorexia and lethargy have been described in several other reports. Most (69%) women whose infants have this disorder had fever during their pregnancy, and 38% had no detectable parasites on smear.[2] *Plasmodium vivax* is now the most commonly observed malarial species in California, reflecting immigration patterns. More than 90% of mothers of these infants whose immigration history is available have been in the United States less than 18 months.[2] The fact that the patient's mother was asymptomatic and without a previous history of malaria is not uncommon.

It is unclear why only one twin has been affected in the five reported cases. In one case, early placental separation and a difficult delivery were implicated as responsible for infection of the second twin.[5] In the only case of monozygotic twins reported, infection was documented only in the first twin and the mother; however, both twins were treated because of the possibility that the second twin had also been infected.[4] In our patient, in whom labor was premature, transmission most likely occurred at the time of delivery, especially because the second twin was the one affected.

The diagnosis of malaria in a neonate is frequently missed, it being usually mistaken for sepsis or infections in the TORCHS syndrome [*to*xoplasmosis, *r*ubella, *c*ytomegalovirus, *h*erpes, and *s*yphilis].[2] In a substantial number of patients, there is a long delay in diagnosis. The incidental finding of parasites by a laboratory technician can clinch the diagnosis, but in cases where there is a low parasite load, diagnosis can be delayed for weeks to months, resulting in substantial morbidity.

In patients who present with jaundice, anemia, fever, lethargy, and hepatosplenomegaly from birth to the first few months of life, malaria should be considered, especially when the infant's mother comes from an endemic area, even in the absence of recent travel. Serologic tests should be done when the peripheral smear is negative and there is a high index of suspicion or when it is not clear how malaria was acquired.

Response to therapy is usually good. In patients like ours, it is important to establish the mode of acquisition because vector-borne infection requires therapy for both the erythrocytic and exoerythrocytic stages, whereas congenital and transfusion-acquired malaria can be cured with treatment of only the erythrocytic stage. The mother received treatment for the exoerythrocytic stage, but the patient did not. The other twin did not require therapy.

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Cardiac Rhabdomyoma With Cardiac Arrest

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PRIMARY CARDIAC TUMORS are uncommon in infants and children. When present, these tumors are usually benign rhabdomyomas that are often associated with tuberous sclerosis.[1,2] Presenting symptoms include obstruction of blood flow and arrhythmias. Rhabdomyomas have also been reported as an incidental postmortem finding in children who died of unrelated causes.[3] We report the case of a previously healthy 18-month-old child who presented with cardiac arrest. Echocardiographic study failed to reveal any structural abnormalities, and the diagnosis of cardiac rhabdomyoma was only established at postmortem examination.

Report of a Case

The patient, an 18-month-old boy, was admitted to the Pediatric Intensive Care Unit (PICU) after being resuscitated from an episode of cardiac arrest at home. The child previously had been entirely well. Minutes after being placed in his crib for a routine nap, he was noted to be making "odd" respiratory noises. He was picked up, awakened, seemed to be comforted, and appeared lethargic but otherwise well. He was placed on the sofa for observation. Within minutes, loud respiratory noises again developed. He was picked up, became limp, and stopped breathing. Cardiopulmonary resuscitation (CPR) was begun by the grandmother and continued by paramedics who arrived within 10 to 15 minutes. An endotracheal tube was introduced, and the child was given 0.05 mg of epinephrine intravenously and transported with ongoing CPR to the nearest emergency department.

On arrival, the child was apneic and had no pulse. Perfusion was reestablished after an additional 0.12 mg of epinephrine and 20 mEq of sodium bicarbonate were administered. The entire duration of the cardiac arrest was estimated at more than 30 minutes.

The child was admitted with a sinus rhythm of 114 beats per minute and a blood pressure of 133/83 mm of mercury while receiving normal saline solution intravenously (IV), but no vasoactive medications. An examination revealed no evidence of trauma or infection. His lungs were clear. The heart sounds were normal, with no third or fourth heart sound or murmur noted. The liver was 1 cm below the right costal margin, and the spleen was not palpable. The pupils were 2 mm and equal, with an equivocal response to light. He had agonal respirations, and cough and gag reflexes were absent. He was flaccid, with no response to pain. His neurologic state did not improve during his hospital stay.

Soon after admission to the PICU, ventricular tachycardia developed, and the patient became asystolic. Cardiopulmonary resuscitation was initiated, with sinus tachycardia returning after the IV administration of 0.1 mg of epinephrine. Once the child was stable, a computed tomographic (CT) scan was done of the head. This showed a small frontal epidural hematoma and a small amount of blood in the falx, findings attributed to his resuscitation and not representative of overt trauma. On return from the CT scan, the child again had the development of ventricular tachycardia, which was successfully treated with IV epinephrine and lidocaine. A lidocaine infusion was started and continued during the remainder of his hospital stay.

The results of admission laboratory studies, including electrolyte analysis, were all within normal limits. He had an atypical electrocardiogram with minor abnormalities in the ST segments in lead II and no R wave noted in V_1 or V_4. Nonconducted ectopic atrial beats were noted as well. An echocardiogram revealed globally poor contractility with no structural abnormalities or discrete masses identified. Mild mitral and tricuspid valve regurgitation was noted.

Over the next day and a half, the patient required increasing pharmacologic support to maintain a blood pressure of 95/50 mm of mercury. During this time, he remained in sinus tachycardia. After he had been in the hospital for 36 hours and while receiving continuous infusions of dopamine hydrochloride (20 μg per kg per minute), dobutamine hydrochloride (20 μg per kg per minute), and epinephrine (1 μg per kg per minute), episodic periods of supraventricular tachycardia and ultimately ventricular fibrillation developed, which were not successfully treated.

At postmortem examination, a 0.5- by 0.5- by 2-cm rhabdomyoma was found in the posterior septal wall of the left ventricle (Figure 1). The cut surface of the myocardium showed areas of subendocardial hemorrhage, but the rest of the heart was structurally normal. No evidence of myocarditis was noted. Examination of the brain showed changes consistent with recent ischemia. No evidence of intracranial trauma or tuberous sclerosis was present. The family was seen in the genetics clinic for counseling, and no evidence of tuberous sclerosis has been found to date.

Discussion

Rhabdomyomas are the most common cardiac tumor of childhood. Cardiac fibromas, although less frequent, are notable for their possible malignant degeneration into fibrosarcomas. Teratomas are the third most com-

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ABBREVIATIONS USED IN TEXT

CPR = cardiopulmonary resuscitation
CT = computed tomography
IV = intravenously
PICU = Pediatric Intensive Care Unit

mon intracardiac tumor. Myxomas, which are the primary cardiac tumors in adults, are distinctly uncommon in children.[4]

A diagnosis of rhabdomyoma can be made on the basis of characteristic echocardiographic findings; histologic proof is not considered necessary.[5,6] Therapy for cardiac tumors is determined by the clinical presentation, and often no intervention is needed. Surgical therapy is considered in patients with severely obstructive blood flow or intractable arrhythmias.[7] In these cases, cardiac catheterization and biopsy are recommended for definitive preoperative diagnosis. Debate continues, however, as to the benefit of surgical intervention because spontaneous regression of these tumors can be expected.

The association of rhabdomyomas and tuberous sclerosis is striking. A 60% prevalence (25 of 43) of cardiac involvement has been reported among children with tuberous sclerosis who underwent routine screening echocardiograms.[1] In only 3 of 17 adults with this disease were tumors identified, however. This discrepancy underscores the tendency for spontaneous regression of many of these tumors. Similarly, in a review of a cohort of patients with cardiac rhabdomyomas, 50% of the children evaluated met criteria for the diagnosis of tuberous sclerosis.[2]

Cardiac rhabdomyomas are recognized as a cause of intractable arrhythmias in children and have also been identified as a cause of fetal arrhythmias.[8,9] Most of the clinical reports describe macroscopic tumors, which can be visualized by echocardiography. Tumors are often multiple and in some cases demonstrate spontaneous regression on follow-up examination.[5,6] Cardiac arrest has been reported as the presenting symptom. There is a case report of a 4½-month-old infant presenting with sudden infant death syndrome who was found to have a 4- by 3-mm cardiac rhabdomyoma at postmortem examination.[10] This tumor was not noted on gross examination when the heart was opened, but was identified on transverse sectioning of the anterior left ventricular wall adjacent to the ventricular septum. Two other cases of healthy children with unidentified cardiac rhabdomyomas who presented with sudden unexplained death are reported in the literature.[11,12] In each of these cases, the diagnosis was made at postmortem examination and was not suspected before death.

The diagnosis of cardiac tumor should be suspected in children with intractable arrhythmias or tuberous sclerosis. The diagnosis should also be considered in patients with an idiopathic cardiac arrest. Whereas an echocardiogram may identify a mass, a normal study does not rule out the possibility of a cardiac tumor. Although the tumor was grossly visible at postmortem examination, echocardiography done before death in our patient failed to identify the presence of the tumor. Review of the echocardiogram by two independent echocardiographers after the pathologic diagnosis was made confirmed the inability to diagnose the tumor with this imaging modality. Other imaging modalities have

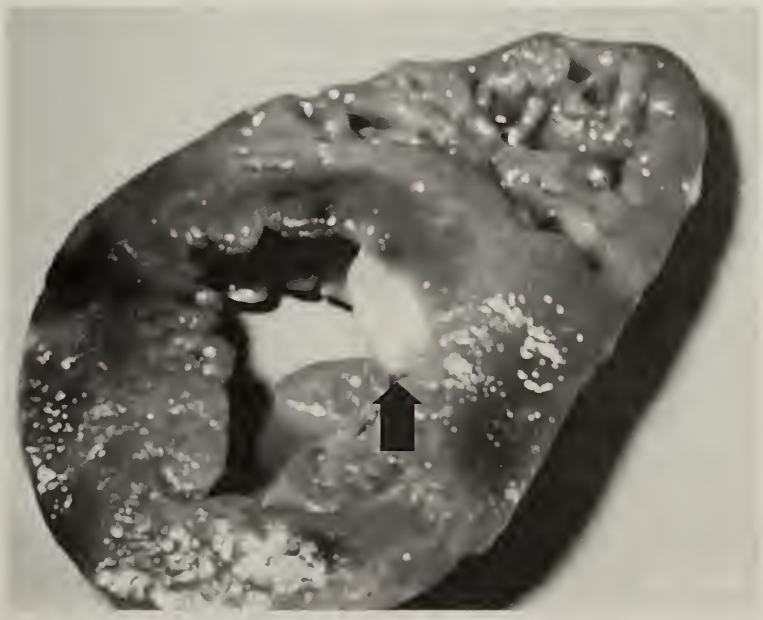

Figure 1.—The gross specimen shows a cardiac rhabdomyoma in the mid- to posterior septal wall of the left ventricle **(arrow)**. It extended from just proximal to the apex to three fourths of the way to the annulus. The surface of the mass was covered by a thin, white portion of endocardium, and the central portion was soft and tan. This mass was not identified by echocardiography.

been used in identifying cardiac tumors, including electrocardiogram-gated CT and magnetic resonance imaging scans. Although the experience in children remains limited, preliminary studies suggest that better resolution may be attained with magnetic resonance imaging than with routine echocardiography.[13,14]

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Topics in Primary Care Medicine

Lesbian Health Care
What a Primary Care Physician Needs to Know

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Many primary care physicians take care of lesbians and women sexually active with women without being aware of their patients' sexual orientation. These women have unique medical and psychosocial needs that each physician must consider. Lesbian identity or being sexually active exclusively with women influences care in areas such as sexually transmitted diseases, risk of human immunodeficiency virus infection, counseling, cancer risk, screening, parenting, depression, alcohol use, and violence. We review an approach to taking a history with all women that facilitates open, comfortable communication with lesbians. We also review specific medical and psychosocial areas of primary care in which caring for lesbians is different from caring for other women. Further research is needed on lesbian health issues to provide appropriate guidelines to clinicians.

(White JC, Levinson W: Lesbian health care—What a primary care physician needs to know. West J Med 1995; 162:463-466)

Busy primary care physicians may see more than 100 patients a week. If physicians estimate that fewer than five of these are lesbian, they may be underidentifying the lesbians in their practice. Knowing the sexual orientation of patients is important to providing high-quality primary care.

History Taking

The dictionary definition of a lesbian is "a female homosexual," meaning a woman who is sexually attracted to other women. For practical purposes, this definition is too narrow because lesbianism is not only a sexual orientation, but also an identity based on psychological responses, cultural values, societal expectations, and a woman's own choices in identity formation.[1-4] Some women call themselves lesbians, but are not sexually active exclusively with women; conversely, some are sexually active with women, but do not identify themselves as lesbian.

Lesbians are a diverse group of women from all racial, economic, geographic, religious, cultural, and age groups. Lesbians are also a diverse group in terms of sexual practices. They may be celibate or sexually active with women or men, or both.[5] Most lesbians are currently either sexually active with women exclusively or are celibate, although in one study, 77% of lesbians had at some point participated in heterosexual coitus.[6] The specific sexual practices of a patient determine her risks of particular diseases and are important in developing individual medical recommendations.

Surveys estimate that 2% to 10% of the population are women sexually active with women.[1,7] Being sexually active exclusively with women and identifying oneself as lesbian influences both the biomedical and the psychosocial aspects of medical care. Primary care physicians need to understand how women sexually active with women are unique with respect to sexually transmitted diseases, the human immunodeficiency virus (HIV), and cancer risk and screening. Women who identify themselves as lesbians also have unique needs with regard to psychosocial issues such as support systems, homophobia, parenting, adolescence, substance abuse, battery, and hate crimes.

Most lesbians defy stereotypes. It is important to realize that any female patient can be lesbian or bisexual. Until physicians know the sexual orientation of their patients, it is important to use language free of heterosexual assumptions. Questions like "What form of birth control do you use?" "Are you married?" and "When was the last time you had intercourse?" set up barriers for a lesbian patient because they assume she is heterosexual. After hearing questions like these, a lesbian may withhold or give false information to protect herself from her physician's possible negative attitudes.[8-18]

There are many nonjudgmental ways to ask about a patient's sexual orientation. We believe the most comfortable time to address the issue is during the social history. Questions such as "Are you in a committed relationship or partnership?" "Are you single, partnered, or married?" "Is your partner a man or a woman?" "Who is in your immediate family?" and "What is your relation-

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ship with your roommate?" can be asked during the social history and do not assume the patient is heterosexual. Questions should be phrased in ways that will assure the patient that her self-disclosure will not produce a negative reaction. Using the social history instead of the sexual history to address sexual orientation removes some of the discomfort associated with talking about sexual activity and provides opportunities to explore patients' social supports as they relate to various illnesses or conditions.

Similarly, during the sexual history taking, it is important not to convey heterosexual bias. The most commonly asked questions are, "When was the last time you had sexual contact?" and "Have you been sexually active with men, women, or both?" Again, because no one can identify every lesbian simply by appearances, it is helpful with all patients to use language free of heterosexual assumptions. Physicians who are unable to convey acceptance or a nonjudgmental attitude toward lesbians might be helped by talking to colleagues or should refer these patients to colleagues who are free of negative attitudes about lesbians.

Medical Issues

Sexually Transmitted Diseases

Sexually transmitted diseases are less common in lesbian patients than in either heterosexual women or gay men. No known gynecologic problems are unique to lesbians, and none occur more often in lesbians than in bisexual or heterosexual women. This may be due in part to the relative epidemiologic isolation of this group from men and the lack of penile-vaginal intercourse among lesbians. Lesbian sexual practices include kissing, breast stimulation, manual and oral stimulation of the genitals and anus, friction of the clitoris against the partner's body, and penetration of the vagina and anus with fingers and devices.[6,19]

Women sexually active with women appear to have a lower incidence of syphilis and gonorrhea than any other group except those who have never been sexually active.[19] Infections with chlamydia, herpesvirus, or human papillomavirus, and pelvic inflammatory disease appear to be uncommon in lesbians who have been sexually active exclusively with women, but all are theoretically transmissible.[6,19,20] Hepatitis A, amebiasis, shigellosis, and helminthism have a low prevalence in lesbians. Hepatitis B occurs only when other risk factors are present.[6,19,20] In contrast, bacterial vaginosis, candidiasis, and *Trichomonas vaginalis* infection do occur in lesbians and appear to be transmissible between women.[6,8,19,21] Based on current data, we do not recommend routinely screening for sexually transmitted diseases in women sexually active exclusively with women. Physicians should survey patients for the most recent heterosexual contact and manage these women and their partners according to the risk of exposure.[22]

Human Immunodeficiency Virus

More than 90% of lesbians with the acquired immunodeficiency syndrome are injection drug users. To date, HIV may have been transmitted between women as a result only of sexual contact in as many as nine cases, but this has not been proved (S. Y. Chu, PhD, MSPH, Centers for Disease Control and Prevention, Division of HIV/AIDS, oral communication, April 1993).[23-25] Exposure to menstrual and traumatic bleeding was probably the source of transmission. The human immunodeficiency virus has been cultured from cervical and vaginal secretions and cervical biopsy specimens taken throughout the menstrual cycle, however.[26] Therefore, it may theoretically be transmitted by infected women who are not bleeding.

Physicians should counsel lesbians to avoid contact with cervical and vaginal secretions, menstrual blood, and blood from vaginal and rectal trauma in all partners, including monogamous partners who have not tested negative for the virus twice within a six-month interval. Methods thought to protect against transmission for orogenital contact include latex squares, known as dental dams, and latex condoms or gloves cut open and laid flat. For vaginal penetration, latex gloves used on hands and condoms on sexual toys may be appropriate. Lesbians who are sexually active with men may become infected with HIV and should use all of the standard safer-sex precautions.

Lesbians who undergo artificial insemination with either fresh semen from donors in the community or frozen semen from sperm banks are also at risk for HIV infection.[27,28] Sperm banks routinely test donors for HIV infection at the time of donation and six months later before releasing the specimen for use. Because of delays in seroconversion, however, it is possible for lesbians to be exposed to HIV with frozen semen or fresh semen from a seronegative donor.[29] Lesbians should avoid fresh semen, especially from donors with an unknown HIV status.

Cancer Risks and Screening

No population-based studies of cancer risk in lesbians have been reported. As a result, screening decisions should be based on individual risk factors using standard screening guidelines for women.

Cervical cancer appears less common among lesbians than among bisexual or heterosexual women, as suggested by lower rates of dysplasia and abnormal Pap smears.[6,20,30] In the absence of specific data, we recommend screening these women every three years, similar to the American Cancer Society's maintenance screening interval.[31] Women with a history of frequent heterosexual contact or another known risk factor should be screened according to published guidelines.

No specific information on breast cancer, endometrial cancer, or ovarian cancer in lesbians is available. Epidemiologic studies suggest an increased risk of breast cancer among nulliparous women, women who are older with their first birth, and women who have never breast-fed.[32,33] Ovarian cancer has been reported to occur more frequently in women who have not used oral contraception and those who have not given birth.[34,35]

Endometrial cancer is also more common in nulliparous women. Many lesbians fall into these categories and may have an increased risk for breast, endometrial, and ovarian cancers. Physicians should follow current guidelines on screening for these cancers where available.

Lesbians older than 40 years report smoking and drinking alcohol more often than their heterosexual counterparts.[36] No data have been reported on lung or head and neck cancers in lesbians. Physicians should emphasize the health risks of smoking and alcohol use in lesbians and strongly encourage smoking cessation.

Psychosocial Issues

A lesbian patient's support network should be elicited to determine her ability to cope with homophobia, illness, and other stressful life events.[37] Societal attitudes toward lesbians may be compounded by a lesbian's own internal homophobia developed from years of living in an intolerant society. Lesbians most often derive support from partners, friends, and lesbian and gay community organizations.[38-40] The quality of the relationship with a partner can be particularly important to a lesbian's psychological well-being.[41] Discord in a lesbian couple can be even more stressful than for a married heterosexual couple because of a lack of traditional social supports.

The process of discovering one's homosexual orientation and revealing it to others, known as "coming out," may begin at any age and may be associated with notable emotional distress.[42] This process has been well described.[43-46] It involves a shift in core identity that takes place in four stages: awareness of homosexual feelings, testing and exploration, identity acceptance, and identity integration and disclosure to others.[47] Prevailing social attitudes influence the experience of coming out.[42,47,48] Internalized and societal homophobia cause a lesbian to perform a sophisticated and fatiguing "cost-benefit" analysis for each situation in which she considers self-disclosure.

Lesbian adolescents are particularly vulnerable to the emotional distress of coming out, and this distress often confounds their developmental tasks.[43] Parental acceptance during this process, especially maternal, may be the primary determinant of the development of healthy self-esteem in adolescent lesbians.[49,50] Signs of confusion about sexual orientation in adolescents may include depression, diminished school performance, alcohol and substance abuse, acting out, and suicidal ideation.[51] In fact, gay and lesbian youth are two to three times more likely to attempt suicide and may account for 30% of completed youth suicides.[52] It is important for primary care professionals to screen adolescents for these signs and to consider confusion about sexual orientation in the differential diagnosis of depression and substance use.

Alcohol use may be as much as three times more common in lesbians than in heterosexual women, although a random sample study found no difference.[19,53-58] As in heterosexual relationships, violence is an issue in lesbians. More than a third of lesbians 22 to 52 years of age have experienced battery by a partner, and alcohol or drug use was involved in most of these incidents.[59] As part of a comprehensive clinical evaluation, primary care professionals should screen all women, including their lesbian patients, for alcohol abuse, depression, and violence.

According to a study for the US Department of Justice, lesbians and gay men may be the most victimized group in the nation.[60] The number of hate or bias crimes against lesbians, including verbal abuse, threats of violence, property damage, physical violence, and murder, is increasing each year.[61-64] Lesbians at universities report being victims of sexual assault twice as frequently as heterosexual women.[65] Perpetrators of hate crimes often include family members and community authorities.[64] Many gay and lesbian adolescents may leave home because of abuse related to their sexual orientation. Primary care professionals should be aware of the possibility that a patient has been a victim of violence, particularly when patients present with symptoms of depression or anxiety.

Parenting plays a role in the lives of many lesbians. Lesbians may have children from previous heterosexual relationships, from adoption, artificial insemination, or heterosexual intercourse, or they may be a foster parent.[9,66,67] Studies have shown no differences between children raised by lesbians and those raised by heterosexual persons.[68-72] Open communication with children about their parents' lesbianism appears important in family function.[70] Some physicians feel uncomfortable performing artificial insemination for lesbians. A physician who feels unable to comply with a patient's wishes should refer the patient to another physician for the service. Primary care physicians can support the pregnant lesbian by demonstrating nonjudgmental attitudes and encouraging acceptance of lesbian motherhood among members of the obstetric team; childbearing classes; and by including partners in the process of conception, prenatal care, and delivery.[66,72]

This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Commentary

Work-Site Health Promotion Programs and Health Care Reform

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About a third of this country's $900 billion-plus medical care costs in 1993 were paid for by employers through employment-linked health insurance, workers' compensation, and other payment mechanisms. Not surprisingly, as medical care costs have increased dramatically in the past two decades, employers have taken steps to try to control their medical care expenditures.

In an effort to reduce employees' need for medical care services, many employers have implemented work-site health promotion and disease prevention programs.[1,2] These programs have proliferated in recent years, and, according to the US Department of Health and Human Services' 1992 National Survey of Worksite Health Promotion Activities, most large employers now conduct work-site–based health promotion programs. Many small and medium-sized employers also sponsor various kinds of work-site wellness activities.

The most common work-site health promotion activities are targeted at smoking cessation, stress management, health risk assessment, cardiovascular risk reduction, weight control, and exercise and fitness.[1,3,4] Other common activities include "backsaver" classes, hypertension detection and treatment, nutrition education, and off-the-job injury control. And now, an increasing number of programs are being developed with secondary prevention in mind, targeting such conditions as complicated pregnancies, diabetes mellitus, arthritis, and long-term pain.

Numerous evaluation studies of these efforts have been conducted in the past several years, and compelling data now show that when these programs are properly planned and implemented, they both improve health outcomes and are cost beneficial.[3-5] According to two review articles, 24 peer-reviewed studies published from 1980 to 1991 and 24 more published from 1991 to 1993[3,4] indicated positive health outcomes relative to smoking cessation, weight loss, and the reduction of coronary heart disease risk factors, as well as improvement in nonmedical areas such as absenteeism and employee morale and retention. Of the 31 studies analyzed to date for cost effectiveness or cost benefit, only 1 failed to indicate a positive return on investment. Evaluations have ranged from six months to six years, with the studies of longest duration, largest number of participants, and randomized clinical trial designs all occurring after 1991. An increasing number of the recent and more rigorously designed studies support earlier studies in showing both health benefits and cost reductions.

From an employer's perspective, some of the most important benefits of work-site health promotion programs are their potential to reduce absenteeism, increase productivity, improve recruitment and retention, heighten employee morale and company loyalty, and enhance public image. For most employers, however, the primary reason for implementing these programs has been to control medical care costs. Despite the other benefits, control of these costs has been management's principal concern.

The control of medical care costs is also the primary motivation for and driving force behind health system reform. A logical question, then, is what effect will reform of the health system have on work-site wellness programs?

All of the recently espoused national health care reform proposals said little or nothing about work-site health promotion. Any successful health care reform scenario—whether national or state—will affect these programs, however.

Because most medium-sized and large employers buy experience-rated health insurance or insure themselves, they would benefit from any medical care cost savings that would accrue from work-site wellness activities—the cost-benefit of such efforts. Under many proposed health system reform scenarios, however, employers will have their medical care benefit payments determined by community rating and formulas for caps and subsidies that are unrelated to their actual experience. In such cases, will employers see diminished value in supporting work-site health promotion activities? Will the other demonstrated economic benefits such as reduced absenteeism and increased productivity be sufficient to justify the continued expense of such activities?

Although the incentives for employers may diminish, the incentives to keep people well under managed care

(Kizer KW, Pelletier KR, Fielding JE: Work-site health promotion programs and health care reform. West J Med 1995; 162:467-468)

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plans will increase under most health system reform scenarios. Some managed care plans already provide a range of health promotion services to their members, but will these plans recognize the potential of using the work site for wellness activities? If so, how will employers work with multiple managed care plans wanting to help organize work-site health promotion programs for their members? And will integrated medical care organizations decide that it is in both their short- and long-term financial interest to sponsor work-site health promotion programs, alone or in concert with employers?

These questions are raised not to argue against health system reform, community-based insurance rating, managed care, or other elements of the likely future medical care system. Rather, they are raised to point out that work-site wellness programs are important to consider in the health system reform discussion, even though they have been largely ignored to date.

Work-site health promotion programs have proved to be effective at improving health outcomes and in controlling medical care costs. The experiences and lessons from these activities should be integrated into more global health care reform proposals so that health system reform really does improve the health of Americans and not just affect a revised medical care payment system.

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Editorial

Management of Diabetes Mellitus After the DCCT—What's Next?

THE RESULTS OF the Diabetes Control and Complications Trial (DCCT) were heralded as potentially the most important advance in diabetes treatment since the introduction of insulin therapy by Banting, Best, and colleagues in 1922.[1] Whether this opinion proves to be pure hyperbole or the DCCT results ultimately have a major effect on diabetes management will depend on many factors, including some that have little to do with the DCCT experiment.

The DCCT was a clinical trial, a human experiment, that was carefully conceived, well funded, and conducted with assiduous attention to detail.[2-4] Although its transference to clinical practice was certainly a goal of the investigators, it was not the primary goal. The primary goal was to do a study that would determine whether intensive therapy, with the aim of achieving glucose levels as close to the normal range as possible, would either prevent or delay the development or slow the progression of the long-term complications of insulin-dependent diabetes mellitus (IDDM). The clinic teams, composed of expert nurses, dietitians, behaviorists, and diabetologists, spared no expense or effort in trying to achieve and maintain glycemia levels in the normal range in the volunteers in the intensive-treatment group. The results of their efforts were manifestly positive, albeit not perfect, based on the substantially lower hemoglobin A_{1c} level maintained by the intensive-treatment group, compared with the conventional-treatment group, throughout the study. Although the level of glycemia did not remain in the absolutely normal range for more than a few of the subjects receiving intensive treatment, intensive therapy profoundly reduced the risk of the development and progression of all of the long-term complications of IDDM.

The approach to intensive therapy in the investigational setting differed fundamentally from that taken in the usual clinical care setting. For example, clinicians rarely have the opportunity to pick and choose their patients, rejecting those who they think will be less compliant and taking only those who are enthusiastic. Moreover, once clinicians accept patients, they rarely, if ever, pursue them with the vigor and attention that investigators in the DCCT did. I doubt that many physicians send telegrams or clinic staff to a patient's home if they miss an appointment. (Many clinicians are secretly relieved when their schedule lightens.) Nor do clinicians manipulate therapies as aggressively or inventively as was done in the DCCT, where many intensive regimens and every conceivable combination of insulins were used to achieve better glucose control. I also doubt that many clinicians use behavioral modification techniques or provide incentives to patients to achieve specific glycemia goals, as was done in the DCCT. Finally, few clinicians have access to the expert treatment teams that were assembled to conduct this trial.

In short, the concerted effort to help patients to achieve the intensive-treatment goals required extraordinary work on the part of a motivated, self-selected group of patients and by a highly skilled treatment team. It would be naive to imagine that the experimental protocol could be translated directly to the clinical setting without considerable effort and changes in the way that diabetes care is usually provided. These comments are not meant to disparage the accomplishments of the DCCT; rather, they are meant to place the DCCT in perspective as a clinical experiment, the translation of which will require effort, will, and resources.

The primary message of the DCCT is that intensive therapy worked. The secondary message, which may be more easily transposed in the clinical setting, is that metabolic control matters. Although purists—of which I am one—will correctly emphasize that the DCCT demonstrated that a specific set of intensive-treatment regimens resulted in a 40% to 76% reduction in the incidence or progression of complications, or both, realists will point out that the intensive treatment was predicated on the glucose hypothesis, that lower levels of glycemia will prevent or attenuate the development of long-term complications. The practical lesson, which is supported by the analysis of the relationship between glycemia and complications derived from DCCT data,[4] is that any lowering of the glycemia level should help to decrease the onset and slow the progression of long-term complications. Thus, rather than abandon patients who cannot perform intensive therapy because of inadequate finances, difficult work schedules, inadequate motivation, or other factors, to their fate, all patients with IDDM should be encouraged to do more. Reducing HbA_{1c} at all levels should reduce the burden of long-term complications.

Whether similar benefits and risks will accrue with intensive therapy for non–insulin-dependent diabetes mellitus (NIDDM), a disease that is enormously more prevalent than IDDM and that is accompanied by similar long-term complications, is unknown. Different authors have come to different conclusions.[5-7] In the absence of any direct data on intensive therapy for NIDDM, defined as treatment methods necessary to achieve near-normal blood glucose levels, it is difficult to be overly enthusiastic or aggressive in these patients. The possible risks of therapy used to achieve normoglycemia in NIDDM are probably trivial if diet and exercise can be effectively employed; on the other hand, pharmacologic therapy, with the risk of hypoglycemia and weight gain, may have profound implications in patients with NIDDM, who have a higher incidence of underlying cardiovascular disease than do patients with IDDM.

The barriers to the performance of intensive therapy that became obvious during the DCCT, such as the prodigious patient effort required, the need for an expert team, and the increased frequency of hypoglycemia, may not be the ultimate threat to its translation. The oncoming wave

of health care reform may wash away any possibility of performing individually designed intensive therapy requiring a team of specialists. Although capitated management may accommodate diseases such as IDDM by including some adjustment for disease severity, it is not clear whether patients with IDDM will be afforded the opportunity to try intensive care. This would be a truly unfortunate result and extremely short-sighted. In the short term, intensive care may be more expensive than conventional therapy, but in terms of the human suffering it prevents, and perhaps in terms of long-term expense, it may be cost saving.

The DCCT may indeed represent the most important clinical advance since the introduction of insulin therapy. Implementation of intensive therapy as practiced in the DCCT will benefit patients who can achieve glycemic goals similar to those in the DCCT. Every effort should be made to implement intensive therapy in as many patients with IDDM as possible. For those patients who cannot perform intensive therapy, either because of limited resources, patient-specific factors, or other reasons, attempts to intensify therapy and lower glycemia are to be encouraged.[8]

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Dietl's Crisis Revisited—The Enigma of Nephroptosis

To the Editor: I would like to report a new twist on an old condition. I am a 32-year-old female physician who is athletic and thin. In January 1993 I began having intermittent abdominal pain that radiated to my back and groin. This was accompanied by a protruding mass on my right side adjacent to the lateral rectus muscle. I went to a surgeon who diagnosed a spigelian hernia. This quarter-sized defect was repaired without difficulty using mesh. After the procedure, I still had a painful mass protruding into the area of repair that was mobile in a vertical plane of about 12 cm. I then went back for a laparoscopic evaluation, but no abnormal masses were seen. After an ultrasonogram, computed tomographic (CT) scan, and intravenous pyelogram, we realized that my kidney was the culprit. The inferior pole was pushing against my abdomen where it had previously herniated. It was highly mobile and at times rotated by 90 degrees on its axis. The CT scan revealed hydronephrosis of my right ureter when lying prone. In an effort to avoid another operation and to get some relief from the pain, I learned how to manipulate the kidney by pushing it up and posteriorly, trying to hold it under my ribs. Between seeing patients, I would lie supine on the floor. When I stood up, my blood pressure would go from 90/60 to 150/90 mm of mercury. Eventually, I had the aberration fixed and have not had problems since.

The results of a literature search left me disillusioned; this condition, once known as Dietl's crisis and which mostly affects women, had been greatly misunderstood.[1] Some surgeons operated on asymptomatic ptotic kidneys in women who actually had other causes of pain.[2] The surgical techniques used in the past were also known to cause complications,[2,3] which led to the idea that repair was futile. McWhinnie and Hamilton took this idea further by concluding that "The predominance of female patients might suggest that this syndrome was the early equivalent of later forms of nonorganic pain," and that "like other ineffective treatments for imaginary disease, surgery for the movable kidney simply faded away."[4 (pp846,847)] As a result of earlier misfortunes of diagnosis and treatment, this anatomic variant, which occurs in 20% of women and 2% to 7% of men,[3,5] is not mentioned in our current texts.

Abnormal renal mobility should be investigated and treated when secondary complications or severe symptoms occur.[2,3,5,6] Information about this condition should be placed back into our kidney and urologic texts to help us diagnose and treat this common anatomic variant, which can cause real, not imaginary, symptoms.

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Can Specialists Practice Primary Care?

To the Editor: Michael Jacobs, MD, in his commentary in the January 1995 issue,[1] attempts to compartmentalize the services of specialists and generalists. But one needs to realize that their roles are the different facets of the same profession, with considerable overlap among their practices. I opted for a primary care year after my internal medicine residency, but then decided to achieve a certain degree of expertise in gastroenterology before beginning my primary care career. Does this mean I will not be a generalist first just because of my rendezvous with a specialty? I love primary care and intend to practice it despite my fellowship training. I see no reason why a generalist like me cannot, at times, be a specialist, too. It's what you practice from the start of your career that matters rather than all this primary care rhetoric that creates an artificial division among specialists and generalists. Retooling, retraining, and rethinking may not apply to the fresh breed of primary care specialists entering the market today.

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* * *

Dr Jacobs Responds

To the Editor: Yes, indeed, Dr Vasireddi is correct in stating that physicians' "roles are the different facets of the same profession," but no, that does not necessarily imply "considerable overlap among their practices." In fact, therein lies my concern.

For those specialists and subspecialists who have dedicated their professional lives to mastering a narrow discipline, switching to a generalist field, with its necessarily broad knowledge base and unique set of behaviors and skills, will undoubtedly lead to frustration. On the other hand, for the many practicing specialist physicians (especially gynecologists and certain internal medicine subspecialists) who already practice and enjoy generalist medicine, I have no problem whatsoever with having them counted in the ranks of primary care physicians.

Dr Vasireddi, despite his "rendezvous with a specialty" but because of his "love [of] primary care" clearly belongs in this latter group. However, until there is evidence to the contrary, I am not as sanguine as he is that our "fresh breed of primary care specialists" shares his affection.

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Guns and Violence—A Second Opinion

To the Editor: As physicians, we should not ever lose our compassion. Yet, we can remain compassionate and still be honest. When it comes to the issue of violence, guns, and self-protection, most medical journals have taken the easy way out of the melee. Instead of providing a balanced and fair approach based on truth and objectivity, the medical literature—and medical organizations—have echoed the emotionalism and rhetoric of the mass media. The constitutional right to keep and bear arms embodied in the Second Amendment must be protected. To preserve our liberty and the tenets of our constitutional republic, we must not jump on the bandwagon of political expediency—and this should include The Western Journal of Medicine.[1]

It is unfortunate that many medical journal editors and writers have joined vociferous administration officials and the entrenched political establishment to propound the public health epidemiologic model to confront the media-tagged issue of guns and violence. This view espouses the erroneous concept of guns and bullets as virulent pathogens that need to be stamped out by limiting gun availability from law-abiding citizens. The only problem is that guns and bullets are inanimate objects that do not conform to Koch's postulates of pathogenicity. Dr Kellermann and others have been known to use the faulty *post hoc, ergo propter hoc*—"after it, therefore because of it"—reasoning, which blames guns for the rise of crime and violence in America. They forget that behind every shooting is a person pulling the trigger who should be held responsible without penalizing the vast majority of citizens who are responsible and law-abiding.

In 1991, 145 children between the ages of 1 and 14 years died of accidental gunshot wounds, 310 children died from suffocation (choking), 1,075 children died from burns, 1,104 died of drowning, and 3,271 died in motor vehicle accidents.[2] These are all tragedies, but do we want to ban food, matches, swimming, and automobiles? The fact is that the firearm accident rates in the United States (including those for children) have been declining steadily since the turn of the century, particularly after 1975, because of the emphasis that has been placed on gun safety education courses.[2]

Edgar Suter, MD, chair of Doctors for Integrity in Research and Public Policy, has reported that the actual costs of treating gunshot wounds in the United States is about $1.5 billion, which is less than 1% of our annual health care expenditures. He points out that estimates of lifetime productivity loss are based on the premise that "every gang banger is a brain surgeon and every rapist a rocket scientist," and that these statistics are, therefore, unreliable.[3(p65)] Dr Suter has published statistics derived from data compiled by criminologists that provide compelling evidence that guns in the hands of law-abiding citizens may potentially "save 75 lives for every one life lost to a gun," and that the benefits of guns are "the lives saved and the injuries prevented, the medical costs saved, and the property protected."[4(p136)]

As far as teenage violence and guns in schools are concerned, more than 20,000 laws pertaining to gun control already proscribe handgun possession by minors and ban guns on school grounds.[5] These laws need to be enforced. Despite all the media hype regarding guns and violence, careful scrutiny of available statistics (FBI Uniform Crime Report, 1992, 1993) shows that there has been a "relatively stable to slightly declining trend [for homicide and gun accident rates] for every segment of American society except for inner city teenagers and young adults primarily involved in illicit drug trafficking."[4(p134)]

The problems of our violent society are not related to an epidemic of inanimate objects, such as guns and bullets, but to deeper and more profound societal problems. What we are experiencing in America today is a crisis of conscience. There is a perfidious trend to absolve the guilty person of responsibility and moral accountability and instead blame society for every illness and affliction. As a result, by default, society picks up the blame and the criminal becomes a victim of circumstances. It is in this atmosphere that draconian gun control measures have been instituted that restrict the law-abiding citizens, but do nothing against the lawbreakers. What we need is a tougher criminal justice system without revolving prison doors and a larger dose of personal responsibility and moral accountability. Strongly needed are principles of moral and spiritual guidance as well as family cohesiveness and major reforms in the criminal justice system.[5]

While I support gun safety education courses and longer prison terms for criminals who commit crimes with guns, I oppose draconian gun control measures that would, in any way, disarm law-abiding citizens and leave them at the mercy of criminal elements who will continue to have guns. Political posturing, giving lip service to political correctness, and jumping on the bandwagon of political expediency are not the answer.

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* * *

Dr Kellermann Responds

To the Editor: The rhetorical excess of Dr Faria's essay is typical of the language used by critics of firearms-related research. Its success depends on painting opponents as extremists. If the argument cannot be won on scientific grounds, alternative strategies must be used. It is obvious that Dr Faria is not a constitutional scholar. Neither am I. But most of us learned in eighth-grade civics that the Supreme Court is the ultimate authority on the meaning of the Constitution, however. Both the supreme court and various federal appellate courts have repeatedly held that federal, state, and local governments can place reasonable limits on firearm ownership (W. E. Burger, "The Meaning, and Distortion, of the Second Amendment." The Keene [NH] Sentinel, November 26, 1991).[1]

It is not necessary for an agent to conform to Koch's postulates to qualify as a public health hazard. Furthermore, it is rarely necessary to ban a hazard to reduce its adverse effects. Motor vehicles and cigarettes are prime examples of both concepts. Car crashes remain a leading cause of death in the United States, but we have been able to substantially reduce the rate of death per million vehicle miles driven through better automobile design, safer roadways, and tougher enforcement of speed limits and drunk-driving laws.[2] We have also made impressive progress in reducing the rate of death from cigarette-related heart disease by educating the public about the health hazards of smoking.[3] Strategies like these could be used to reduce many firearm-related injuries and deaths as well.[4]

At two points in his essay, Faria refers to "draconian" gun control laws in the United States. Which laws does he consider draconian? Is a waiting period and criminal background check draconian? Are laws that restrict handgun purchases to one a month draconian? Are laws that outlaw the sale of handguns to minors draconian? Is any gun control law reasonable, or should all of them be abolished?

Physicians can and should play a key role in responding to the growing problem of firearm-related violence. Faria's comments remind us how far we have to go.

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Medical Costs Then and Now

To the Editor: Thank you for publishing the interesting commentary by Michael J. Hennessy, MD, regarding the thyroid operations on his grandmother.[1] In 1907 one of the Drs Mayo performed a successful thyroidectomy in the face of thyroid storm by immersing the patient in an ice bath. He operated on a recurrence 30 years later for the same fee.

The value of money has changed so much during the interim that the size of those fees may not be clear to some readers. It's a little hard to measure inflation accurately, as we buy different things at different times. In 1907, however, an eight-room house could probably have been bought for $3,000, a woolen suit for $4, and a large glass of beer for a nickel (sometimes with free snacks). From such numbers, it is likely that prices have risen 40- to 50-fold. Thus, Dr Mayo's surgeon's bill of $240 would be equivalent to perhaps $10,000 today.

The 1937 fee of $240 can be related to a worker's income of about $1,200. When my father took me to see the circus train unload in 1940, I bought a hamburger for a nickel, although his cost ten cents. Our maid was paid $260 a year plus board and room. It looks as though surgeons' incomes have been going backwards for 90 years. By any calculation, hospital charges have been moving in the opposite direction.

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* * *

Dr Hennessy Responds

To the Editor: I want to thank Dr Burdick for his observations and perspective regarding turn-of-the-century medical costs. There was indeed a time when a nickel candy bar cost five cents.

The point of my article was fiscal vigilance. When direct exchange of money occurred between patient and physician, the value of service could be directly judged. The fiscal intermediary of health insurance and the myriad systems of managed care clouds the issue for patients. We enter an era in which profit is taken from those who request medical care and those who provide medical care. Administrative costs and shareholder profits threaten to erode our medical resources. Within our

organizations and as individual physicians, we must demand "fair" distribution.

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Lead Poisoning Alert—False Alarm?

To the Editor: The childhood lead poisoning review by Landrigan and Todd in your August 1994 issue is misleading, and the accompanying editorial implies that symptomatic lead poisoning is widespread.[1,2] Clinicians are aware that following implementation of the anti-lead legislation of the 1970s, symptomatic lead poisoning has been rapidly disappearing because of logarithmically plummeting blood lead levels. The recent National Health and Nutrition Examination Surveys (NHANES III) found more than a fourfold decrease (from 12.6 μg per dl to 2.8 μg per dl) in the mean blood lead level of the United States population from 1986 through 1991 compared with the mean level from 1976 through 1980.[3,4] A 10-fold fall in the prevalence of blood lead levels of 10 μg per dl or higher (from 88.5% to 8.9%) and a 20-fold fall (from 24.7% to 1.1%) in blood lead levels of 20 μg per dl or higher occurred from 1976 to 1991.

Evidence that low blood lead levels (<20 μg per dl) cause subclinical neurobehavioral defects is inconclusive and contradictory; studies are complicated by confounding variables, small effect size, and imprecise outcome measures. Recent research showed no ill effects of low blood lead levels in toddlers in a developing country.[5]

Effects of low lead levels have been exaggerated. A recent epidemiologic review by Pocock and colleagues showed that neonatal lead exposure had no effect on childhood IQ and that lead exposure in the first years of life had a slight effect (1 to 2 IQ points).[6] Alternative explanations for this small effect, including reverse causality, must be considered, however. The review indicates that the priority of childhood lead detection and intervention is debatable.[6]

Universal childhood lead screening risks falsely labeling normal children as brain damaged. Falsely high blood lead levels are common, particularly when capillary blood is used. No evidence exists that chelation therapy benefits children with low or moderately elevated lead levels,[2] and this treatment might cause harm. Experience with the new oral chelator meso-2,3-dimercaptosuccinic acid (succimer [DMSA]) is limited; caution in its use is advised. Improper lead abatement has elevated blood lead levels in children. A multibillion-dollar, publicly financed industry in lead screening and abatement is burgeoning. Landlords are abandoning low-cost housing because of increasing liability, which will increase homelessness.

Public education about childhood lead poisoning and screening of high-risk groups should be encouraged, but diverting billions of dollars to address a disappearing problem of questionable importance is wasteful. Our child health care resources are better spent addressing critical health deficiencies such as violence, noncompliance with immunization, child abuse, teenaged pregnancy, drug and alcohol use, prematurity, homelessness, and pediatric acquired immunodeficiency syndrome.

Acknowledgment

The Medical Editing Department, Kaiser Foundation Research Institute, provided editorial assistance.

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Drs Landrigan and Todd Respond

To the Editor: Dr Schoen argues that lead at low blood levels is not toxic to children and that there is therefore no need to screen children for lead. Dr Schoen's scholarship in support of these arguments is highly selective. His reasoning is faulty. And his conclusions are wrong.

Four extraordinarily well-conducted, prospective epidemiologic studies have shown that blood lead levels in the range of 10 to 20 μg per dl are associated with neurologic and behavioral impairment in children.[1-4] Data from these studies form the basis for current recommendations from the Centers for Disease Control and Prevention (CDC) on childhood lead screening.

The replication of original results in multiple studies undertaken by different investigators in different populations at different times and under different circumstances constitutes the strongest evidence of causality in epidemiologic research. This criterion of replicability has been amply fulfilled in the analysis of low-level lead toxicity. The above-cited studies were undertaken among white American children in Boston, Massachusetts,[1] African-American children in Cincinnati, Ohio,[2] Australian children in Port Pirie, Australia,[3] and Croatian children in northern Yugoslavia.[4] All have shown that blood lead levels in the range of 10 to 20 μg per dl are associated with subclinical neurologic and behavioral dysfunction. Moreover, these studies have undergone detailed independent review by the CDC[5] and by the United States National Academy of Sciences.[6] Both of these distinguished bodies have concurred in the principal conclusion of those studies, and they have determined that blood lead levels between 10 and 20 μg per dl are causally associated in young children with per-

manent loss of neurologic function and permanent impairment of behavior.

In his letter, Schoen chooses not to cite any of those reports and commentaries. Instead, to rebut the premise that lead is toxic to children, he refers to only one recent article from a developing country.[7] Also, he cites a review that actually concludes that "the evidence strongly supports an inverse association between body lead burden and child I.Q."[8] In our view, this is evidence of selective scholarship. It does not constitute a balanced or thorough appraisal of the scientific literature.

Schoen argues that universal screening of children for lead risks falsely labeling normal children as brain damaged. This argument misses the point that the purpose of screening is to prevent lifelong neurologic and psychological impairment. Identifying children with elevated blood lead levels can lead to effective prevention. In more than 90% of such cases, intervention consists of nothing more than identifying and abating a child's environmental sources of lead.

Reducing blood lead levels in the American population represents one of the great modern successes of public health. Schoen is correct in noting that a reduction of more than 80% in the average American blood lead level has been achieved over the past 15 years. This success has been accomplished principally by the removal of lead from gasoline.

The problem of childhood lead poisoning is still with us, however. The CDC estimates that, even in the wake of the recent reductions in lead exposure, 1.7 million preschool children in the United States continue to have blood lead levels above 10 μg per dl.[9,10] Moreover, these elevated blood lead levels are to be found among young children in every geographic region of the United States and in every socioeconomic stratum. To be sure, rates of lead poisoning are highest in poor, minority, inner-city children living in the Northeast and North-Central states. But numerous cases of lead poisoning have been reported in all regions of the United States, including the Pacific Coast. Cases also have been reported in families of higher socioeconomic status who live in older homes or who became involved in home renovations that released lead dust.[11]

A common fallacy in medicine is to assume that no problem exists when no problem has been sought. Schoen seems to fall into this trap when he argues that lead poisoning is not a problem in many areas of the United States. In reality, however, no systematic assessment of blood lead levels has ever been undertaken among children in many regions of this country.

We would argue that either universal screening or a statistically rigorous sampling of blood lead levels among children in every census tract in the United States represents a reasonable interim strategy for the next several years. The results of such screening should be meticulously collected and analyzed by the CDC. If certain areas of the United States are found to be truly free of a lead poisoning problem, then more targeted screening could be undertaken. But in the absence of good baseline data, Schoen's proposal to undertake neither universal screening nor universal sampling of children is ill-founded and perilous.

Current national strategies for screening of young children for lead have been developed by the CDC with painstaking care and are founded on diligent review of the literature.[5] To dismiss these well-crafted strategies on the basis of Schoen's skewed and selective analysis would represent neither good pediatrics nor good sense.

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Dr Osterloh Responds

To the Editor: Weak neurocognitive and neurodevelopmental effects of environmental lead at low blood lead levels have been statistically inferred through epidemiologic studies in small populations of children. These low-dose effects are consistent with the effects of lead at higher doses, with animal studies, and with investigations on cellular neurologic growth. Because these effects are subclinical and measurable only when populations of children are studied, it is prudent to investigate and regulate lead exposure for the health and safety of this population.

The letter by Schoen states that the observed neurobehavioral effects are inconclusive and contradictory and that some studies indicate no effect. As with all of science, this will be the case. Consensus of a number of panels and agencies has concluded that there is a consistent effect of lead. The review cited by Schoen shows

that 21 of 26 prospective and cross-sectional studies done after 1979 demonstrate a lowering of IQ scores.[1] Although a remarkable job was done in homogenizing these studies, outcomes in the prospective studies were delimited (for congruity) to only Wechsler IQ scales assessed at 5 years of age. Thereby, neurobehavioral measures were omitted from earlier ages that used Bailey mental index scores. Some of the prospective trials showed greater changes in scores at earlier ages when the developing neurologic system is thought to be most susceptible. In limiting assessment to 5-year-old outcomes, further confounding is allowed due to the influence of education and compensatory adaptation that would occur between noted exposure and assessment. Hence, the confidence limits of the change in test scores were shown to include zero for most of these studies using this end point. The authors, however, definitively state, "Our overall synthesis of this evidence in all 26 studies strongly supports an inverse association between body lead burden and child IQ."[1(p1195)] Schoen contradicts himself by stating that this review by Pocock and colleagues showed no effect on childhood IQ, but then adds that the effect is only slight. He is missing the point. This slight effect is the issue. Preventing it is possible. Ameliorating lead's effects may not be as easy.[2]

Schoen states that my editorial implied that "symptomatic lead poisoning is widespread." He is incorrect. This is neither the case nor stated as such. He is also concerned about the risk of "falsely labeling normal children as being brain damaged." There can be no prediction or observation of neurologic injury from an individual low blood lead level (that is, 10 to 25 μg per dl), only an estimate of risk, which public health authorities would like to prevent. Screening is a method of finding cases to prevent further exposure. Universal screening is not likely to be recommended further because a number of surveys indicate that only a low proportion of the general population is at risk. The Centers for Disease Control and Prevention will likely issue new guidelines in this direction.

Unique childhood exposures to lead can be found in almost any population. Screening will help locate these exposures and allow prevention. It can be argued that a population approach should be taken in preventing these effects because the effects of lead at these low blood lead levels are demonstrable only in populations. Thus, pediatricians such as Schoen may object to the implementation of lead screening on patients in busy pediatric practices. In the debate over blood lead screening, such questions and emotional issues arise around the cost and time that are devoted to screening activities and the lack of true effective interventions—that is, to reverse neurobehavioral deficits—at these low blood lead levels. The double entendre of the editorial title calls attention to both sides of this problem.

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CORRECTION

In the February 1995 issue, David A. Fisher, MD, is listed as affiliated with the Departments of Medicine at the University of Califorina, San Francisco, and Davis, Schools of Medicine.[1] He is affiliated with the Department of Dermatology at those institutions.

The Editors

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Radiologic Case

Gallium Citrate Ga 67 Scanning in Acute Renal Failure

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A 65-year-old woman was admitted because of acute renal failure, manifested by a blood urea nitrogen value of 32.0 mmol per liter (89 mg per dl) and a serum creatinine level of 750 μmol per liter (8.5 mg per dl). She had had vague fatigue with muscle and joint aches approximately two months earlier. A week before admission, she had chest tightness, wheezing, and shortness of breath after a single dose of cefaclor with a dental procedure. She reported a decreased urine volume for three or four days in the week before admission and nausea, loose stools, and fatigue. She took hydrochlorothiazide daily for a year for hypertension, but had no history of renal disease. A year earlier, a routine blood urea nitrogen level was 3.5 mmol per liter (10.1 mg per dl), and a serum creatinine was 90 μmol per liter (1 mg per dl).

On examination, she had a macular rash on her back and mild orthostatic hypotension. Her leukocyte differential count showed 0.05 (5%) peripheral eosinophils, and eosinophils were found on a Hansel stain of the urine. All medications were stopped, and a gallium scan of the kidneys was initiated (Figures 1 and 2).

What is the most likely diagnosis?

What are the most common causes of this disorder?

What abnormality is seen on the gallium scan, and what diagnoses are suggested?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A gallium citrate Ga 67 scan in a patient with acute renal failure shows normal uptake in the kidneys at 24 hours.

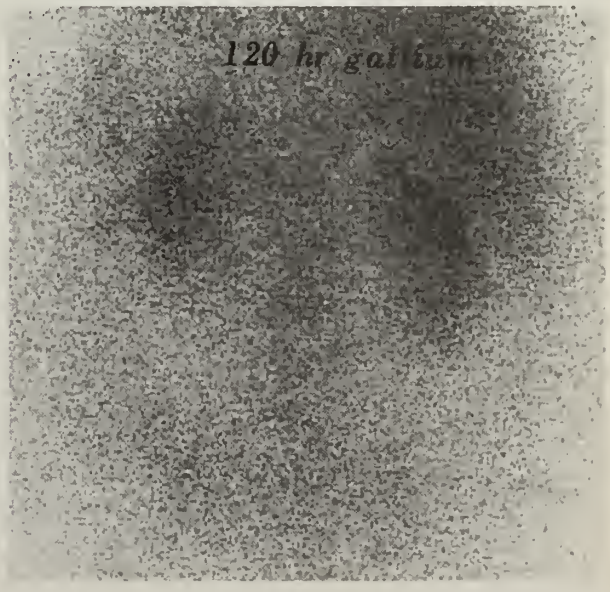

Figure 2.—A gallium citrate Ga 67 scan of the same patient at 104 hours shows abnormal (persistent) uptake.

(Border WA, Holbrook JH, Peterson MC: Gallium citrate Ga 67 scanning in acute renal failure. West J Med 1995; 162:477-478)

From the Divisions of Nephrology (Dr Border) and General Internal Medicine (Dr Holbrook), University of Utah Medical Center, and the Department of Medicine, LDS Hospital (Dr Peterson), Salt Lake City, Utah.

Reprint requests to Michael C. Peterson, MD, Nephi Medical Clinic, 346 E 600 North, Nephi, UT 84648.

ANSWER: Acute interstitial nephritis

ACUTE INTERSTITIAL NEPHRITIS is an increasingly recognized cause of acute renal failure. The symptoms and signs of this disorder are nonspecific and include fever, arthralgia, rash, fatigue, and gastrointestinal upset. The laboratory analysis may reveal azotemia, peripheral eosinophilia, elevated erythrocyte sedimentation rate, and microscopic hematuria, proteinuria, and eosinophils in the urine.

A number of drugs are associated with acute interstitial nephritis. The list includes but is not limited to penicillins such as methicillin, nafcillin, oxacillin, and penicillin G; nonsteroidal anti-inflammatory drugs such as naproxen, ibuprofen, indomethacin, and mefenamate; cephalosporins, cimetidine, rifampin, erythromycin, fluoroquinolones, thiazides, and allopurinol.[1-3]

On renal biopsy, there is interstitial edema, and a mononuclear cell infiltrate is found invading the interstitium. Most of the cells are lymphocytes; there are smaller numbers of plasma cells, monocytes, eosinophils, and neutrophils. The tubules are involved, and severe tubular damage may occur. The glomeruli and vessels are spared.[1,3,4]

The most important aspect of the treatment of acute interstitial nephritis is withdrawal of the offending agent; other supportive care such as dialysis may be needed, and in some cases, administering steroids may be useful. Anecdotal reports speak both for and against steroid use. The typical course of acute interstitial nephritis is complete or near-complete resolution of renal function following withdrawal of the offending agent.

Gallium scanning often reveals persistent uptake in the kidneys at 48 hours or longer in patients with acute interstitial nephritis. In patients with acute renal failure, persistent uptake of gallium citrate Ga 67 in the kidneys suggests an inflammatory process such as acute interstitial nephritis or glomerulonephritis, and a normal gallium scan points to a noninflammatory process such as acute tubular necrosis or obstruction.[2,5] Gallium scintigraphy does not produce reliably abnormal results in patients with chronic interstitial nephritis.[6]

The diagnosis of this disorder ought to be based clinically on a characteristic constellation of symptoms in a patient taking a drug known to cause the disease. Findings of a physical examination should not suggest another cause of acute renal failure, and the laboratory results ought to help confirm the diagnosis. In patients with a characteristic clinical picture, it may not be necessary to do a renal biopsy or a gallium scan. The clinical usefulness of a gallium scan in acute renal failure may lie in being able to avoid the cost and risk of renal biopsy in certain patients whose diagnosis is not clear.

In our patient, the isotope and gallium scan cost $579, not including a radiologist's fees (personal communication, nuclear medicine scheduling and information office). This is several times less costly than a renal biopsy.

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Lessons From the Practice

Images

SAMUEL M. CHEN, MD, *Glendale, California*

I see images of black and white and shades in between. They are images of a woman, standing. Now she faces me; now I see her profile. Her arms are out a bit on the first image, uplifted on the second. I actually see only part of her—her upper torso. Briefly, I wonder what she looks like. But it is too late; she is gone. Besides, the images I see are not those of a photographer. Mine are of what lies beneath the surface, hidden from the camera and the eye. I am reminded of the truism that beauty is only skin deep. Although few persons look alike externally, there is less variation on the inside. I sit a moment, gazing, guessing how much body fat there is, before I really look, which is my job.

When I do look, I immediately spot the intruder. Something is there that does not belong—a stranger who came, uninvited, and stayed. I see a blot of gray where there should be none, containing a line demarcating fluid and air. It is enclosed within a sphere the size of a tennis ball. But the walls of this tennis ball are thick, and the lining is irregular. I worry.

I also wonder how long it has been there. I think it is too bad it is on the inside. Surely she would have come sooner had it been on the outside. Maybe it will be OK yet, something that has come to stay only for a short while. I hope. Even though I do not know her, I would not wish this stranger, this thing, on anyone. I remember hearing a slight cough from a nearby room earlier. Maybe the cough and these images go together.

I almost forget about her until her attending physician brings her images to me for review. I reiterate my concern and wish we could see beyond the shades of gray without invading her further. This time I do not forget her, but file her in the back of the cabinet of my mind.

Until, shortly thereafter, a surgeon once again brings her images to me, and I sense the nearing of the dénouement. While I fear the knife, both for her (because of what she is about to undergo) and for myself (because I may turn out to be wrong), I am glad this knife-wielder will do the cutting. His touch is deft and his judgment sound.

This time I learn that she is the wife of one of my children's teachers. At once the sense of community heightens, and my world shrinks a little. She moves up to the front of the filing cabinet.

She is not able to tolerate removal of a lung, should that be necessary for cure, for childhood infections have damaged both lungs. The surgeon, skilled and concerned, does his best, but his fingers are crossed when he emerges from the operating room.

Time tells with a vengeance. A few months later, images of her chest show new gray areas. The stranger has returned.

Now we meet. She has declined chemotherapy, having had acquaintances who died despite the drugs, and perhaps made the more miserable for having taken them. She has learned of an out-of-state physician who treats with "natural" methods and wants to know more. I see the figure behind the images, a still-attractive woman, prematurely aged by pain and disease, nevertheless in good spirits. I hurt for her and hope we are doing the right thing. Her family physician, while not enthusiastic, does not oppose her decision. For this I am grateful.

After one visit to the new physician, she and her husband are convinced that his is the path they wish to follow. It is not feasible for them to remain out of state, nor can they return to him for frequent visits. They ask me to assist in obtaining the recommended medications.

I have seen this physician in action and am unsure about his unconventional methods. Whether they provide benefit I do not know, but I doubt they cause serious harm. I agree to help her.

The program consists of several medicines, easily obtained. The mainstay is megadoses of vitamin C, administered intravenously in her home twice a day for weeks. We improvise: a bent coat hanger secures the IV bottle. Thoughts of jungle medicine fleetingly cross my mind. She is ever cheerful and grateful, her husband supportive; both mask inevitable apprehension.

The stranger stays, though apparently content to rest a while before becoming more obtrusive. Gradually she requires oxygen, then more oxygen. Pneumonia develops, which almost finishes her. But her spirit is strong, and that counts for something. Nature seems to say, I will respect you, since you respect me.

She lasts almost a year from the time of diagnosis, leaving us quietly from the greater comfort of a hospital bed. I sit with her from time to time and wonder why this happened. She is in her 50s, did not smoke, and had no obvious risk factors for cancer. I also wonder if what we did was best, given the tough choices. Then I recall a few things—that this is what she and her family wanted, that she was able to see her latest grandchild born a few months before her death, and that she was at peace throughout her ordeal—and I am able to sleep at night.

(Chen SM: Images. West J Med 1995; 162:479)

Dr Chen is a radiologist in private practice in Glendale, California.
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Lessons From the Practice

Having a Good Time

Please Remember to Do the Same

FRED A. LONDON, MD, *San Francisco, California*

Years ago, a nice young woman of about 35 would come see me for her yearly checkups. She was perfectly healthy, and after the examination, we would chat about a variety of things. I would order a minimum number of tests, and then I would make an appointment to see her the following year. She was vivacious and interesting, and I looked forward to her visits. She took birth control pills, and although she did not smoke and had no predisposing risk factors, one day she came into our emergency department with a right-sided cerebrovascular accident and a mild aphasia. Fortunately, she recovered the use of the right side of her body and was left with only a trace of a speech impediment.

A short time after her recovery, she decided to move to Hawaii. After she settled in, she sent me a postcard thanking me for my efforts to help her. The postcard had a picture of three roughly drawn animals: a large dog, a slightly smaller cat, and an even smaller bird. On the body of the dog was written, "Nothing really matters," on the body of the cat was written, "Except a few things," and on the body of the bird was written, "That really don't matter very much."

Over the past 20 years, I have kept the postcard taped to a bookcase, so that I can easily see it as I enter my consulting room, and it constantly reminds me of what is important and what is not. It is there along with a picture of Osler, Halsted, Kelly, and Welch.

About a year after I received the postcard, I had a patient in the office who had many, many worries. He was worried about his business, his marriage, his kids, and many other things that I no longer remember. But I do remember telling him to wait while I went out of the examining room, hurried down the hall to my consulting room door, and peeled the postcard off to show it to him. He looked at the postcard, read it carefully, then slowly turned to me, and, with the first smile I had seen on his face, said "I am responsible for this postcard. You see, my company produces these cards, and I personally created this one." I explained the importance of the card to me and how it had been sent to me by a former patient. We talked a bit, and then he left. Shortly afterward, he moved his company and his family to Santa Barbara, so I cannot tell you if he ever took his own wonderful advice. Still, I keep the postcard next to Osler and company, and when there is more than the usual confusion in my office, when charts cannot be found, when I have been double-booked, when the x-ray film reports are not available, I sometimes stop and look at that wonderful postcard. When I do, I thank God for the opportunity to meet so many people who have so much to teach me.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(London FA: Having a good time—Please remember to do the same. West J Med 1995; 162:480)

From the Permanente Medical Group, San Francisco, California.
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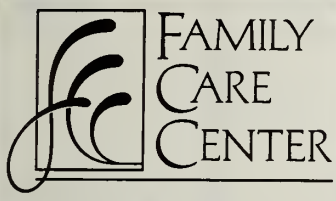

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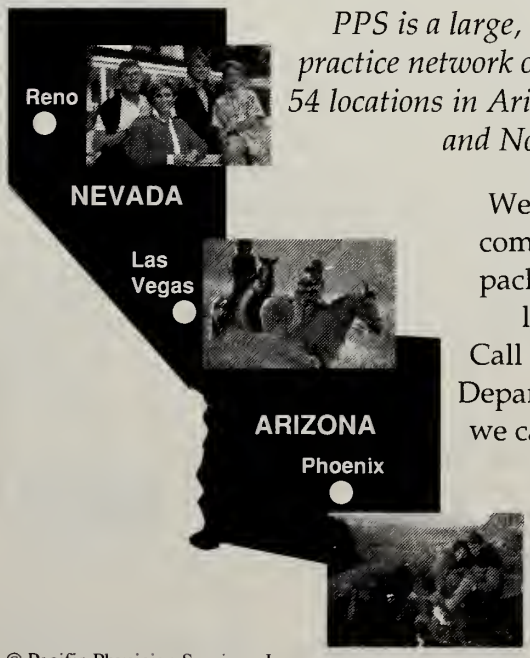

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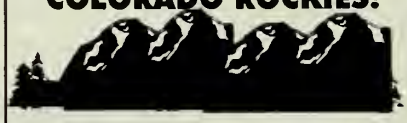

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 1-5, 1996, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 7-10, 1995, The Ritz Carlton Hotel, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Four Seasons Hotel, Newport Beach, CA.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. May 10-11, 1996, New Mexico Medical Society, Albuquerque, and Holiday Inn, Pyramid.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 27-30, 1995. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 28-30, 1995. Spokane Sheraton Hotel, Spokane, Washington.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: **June 15-17**, 1995, Jackson Lake Lodge, Moran.

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1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. 2. *Clinical Efficacy Update II*, SmithKline Beecham Pharmaceuticals, 1994

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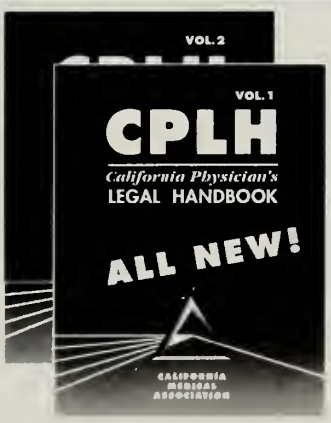
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above Once results are known, adjust therapy, if appropriate
Contraindications: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide) These have generally been cases associated with serious underlying diseases or concomitant medications (see CONTRAINDICATIONS and ADVERSE REACTIONS--*Liver*)
Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy
A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently
Augmentin should not be coadministered with Antabuse® (disulfiram).
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential
Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin* There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman
Adverse Reactions: *Augmentin* is generally well tolerated The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of them. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued The hepatic dysfunction, which may be severe, is usually reversible On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin* Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely
BRS-AG L8A

CMA's 1995 Legal Update



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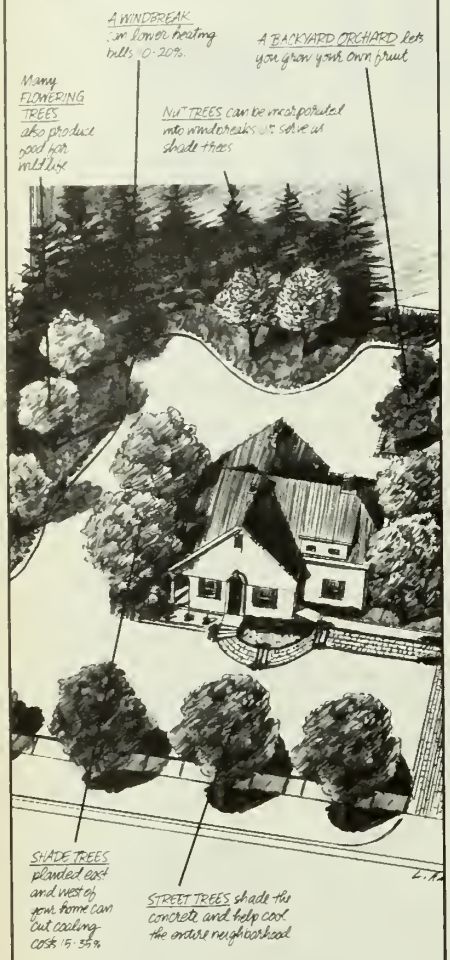

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Articles

Health Care Cost Effects of Public Use of a Regional Poison Control Center

THOMAS E. KEARNEY, PharmD; KENT R. OLSON, MD; LISA A. BERO, PhD;
STUART E. HEARD, PharmD; *and* PAUL D. BLANC, MD, *San Francisco, California*

Poison control centers in the United States are threatened with closure, and attempts at a cost-benefit analysis of these services have been indeterminate. The purpose of this study was to compare the operating costs of a regional poison control center resulting from public use of its telephone hotline services with those of hypothetical alternative sources of advice and care. We conducted a follow-up telephone survey among 589 public callers to the San Francisco Bay Area Regional Poison Control Center who had been managed at home without medical referral after an unintentional poisoning. All survey respondents were asked what alternative action they would have taken had the poison control center not been available to assist them by telephone consultation. We then surveyed emergency departments and physicians' offices cited as alternatives by the callers to determine their response and charges for evaluating a suspected poisoning case. A total of 464 (79%) of the callers surveyed would have sought assistance from their local emergency health care system had the poison control center not been available. We conservatively estimated that the total charges for such evaluations would be $71,900. Comparatively, the total actual operating cost of services provided by the poison control center for all 589 poisoning cases was $13,547. Most of the study subjects (429 [73%]) had private insurance coverage. Direct public access to these services probably reduces the use of emergency health care resources, thus lowering health care costs.

(Kearney TE, Olson KR, Bero LA, Heard SE, Blanc PD: Health care cost effects of public use of a regional poison control center. West J Med 1995; 162:499-504)

Poison control centers nationwide are threatened with closure as state and local governments and community hospitals have reduced financial support. The ensuing policy debate has centered on the costs and benefits of these services. Poison control centers manage most cases of poisoning by providing telephone advice to a caregiver at home, obviating the need for evaluation or treatment at a health care facility.[1]* We hypothesize that the loss of poison control center services could lead to major cost increases as poisoning victims overuse other, more expensive, emergency medical services (911 and local emergency departments).

Quantifying the costs and benefits of poison control centers has been difficult, however. Earlier studies have suggested that most people, in the absence of poison control center services, would indeed seek an emergency department evaluation in the face of a possibly toxic exposure, irrespective of the nature of the poisoning.[2-7] Moreover, these increased emergency department evaluations often would be accompanied by the use of 911 and ambulance systems. These earlier studies have been limited by possible recall bias and incomplete cost estimates. To address these shortcomings, we interviewed study subjects within a short time after a poisoning encounter and directly surveyed health care providers cited by interview subjects as alternative caregivers in the event poison center hotline services were unavailable. From this follow-up survey, we ascertained directly from providers their standard management approaches and charges for such alternative care.

*See also the editorial by Toby Litovitz, MD, "Listen, Ye Legislators, Our Children Need You!" on pages 552-553 of this issue.

Cases and Methods

Poison Control Center Study Site

The San Francisco Bay Area Regional Poison Control Center (PCC) has been in operation since 1979

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ABBREVIATIONS USED IN TEXT

HMO = health maintenance organization
PCC = San Francisco Bay Area Regional Poison Control Center

and is certified by and operated as a regional poison control center meeting the criteria set by the American Association of Poison Control Centers.[8] It is also designated by the California Emergency Medical Services Authority to serve a ten-county region encompassing the San Francisco Bay Area and North Coast counties, with about 4.4 million residents. The PCC telephone hotline is staffed on a 24-hour basis by licensed doctoral level (PharmD) clinical pharmacists who are certified as Specialists in Poison Information. They provide emergency information and telephone treatment advice regarding the toxicity of household products, drugs, and environmental chemicals involved in human exposures. Specialized physician backup is available on a 24-hour basis. Callers to the PCC include the general public, which has direct access by a toll-free telephone number, and professional health care providers seeking case-management advice.

During the calendar year when this study was performed (1991), the PCC handled 46,641 exposure calls, of which 34,766 (74%) were from public callers at a private residence. Of these, the majority, 25,563 (55%), concerned poisonings in children younger than 5 years. A total of 33,669 (72%) cases were managed entirely at home after PCC consultation to a caregiver (most frequently the mother of an exposed child). All cases of human poison exposures reported to the PCC were computerized using a customized data collection system. Cases entered into this system met all specifications, audit variables, and had an acceptable quality factor for the American Association of Poison Control Centers' National Data Collection System.[1]

During fiscal year 1991-1992, the PCC had a total operating budget of $1.08 million. Of this, approximately 70% covered salaries and telephone expenses for the hotline staff. The ratio of exposure calls per staff member was 4,664 annually.

Interview of Callers to the Poison Control Center

We conducted a prospective telephone survey of public callers to the PCC using a brief standardized interview schedule. This study was approved by the Committee on Human Research, University of California, San Francisco. All interviews were carried out by a single trained surveyor. We identified interview subjects from a computer-generated list of PCC callers by selecting all even-numbered case log numbers over a six-week period.

We employed the following inclusion criteria: the PCC call was from a private home with a valid telephone number, the actual exposure site was also a private residence (as opposed to a school, workplace, or hospital), and the poisoning was managed entirely at a private residence. We excluded non–English-speaking callers and any possible interview subjects not successfully reached within 72 hours of the initial PCC contact. Although the PCC caller could have been the poisoning victim, in most cases the caller was a caregiver (such as the parent of an exposed child).

We coded into categorical scenarios answers to the following open-ended question: "If you could not have reached the San Francisco Poison Control Center when you called after [name of patient] was poisoned, what would you have done?" We also asked the caregiver whether they would have provided first aid if professional advice could not be obtained. To identify who would be liable for costs incurred, we asked what type of insurance coverage the poisoned person had.

Interview of Health Care Professionals

We also conducted a structured telephone survey of hospital emergency departments and private medical offices that were identified as the sites of choice if the PCC were not available. This follow-up survey of health care professionals was conducted using an independent surveyor and a standardized questionnaire. Open-ended responses were coded into categorical variables. We determined who on site usually answers incoming calls from the public, whether or not the emergency department or office had a policy regarding how to handle a public poisoning call from a private residence, and what the provider would have recommended to the caller if the PCC were not available.

Estimation of Charges

We estimated the charges for emergency department and private physicians' office visits during calendar year 1992. In each of the ten counties served by the PCC, we ascertained charges at two health care facilities (an emergency department and a private physician's office) chosen at random from among those identified in the health care survey. We ascertained charges for basic office or emergency department visitation for a medical consultation by the physician and, for emergency department visitations, the separate physician charges incurred if not included in the basic visitation charge. Because most of the cases were children, we applied the conservative measure of pediatric rather than adult charges in all cases. We did not include laboratory, prolonged observation or monitoring, or pharmaceutical charges. We also surveyed an ambulance service in each county to determine the basic transportation charges for a unit with advanced-life-support capabilities. We computed survey responses that cited nonphysician health care professionals (such as pharmacists, nurses) as "free of charge."

The estimated average cost of non–PCC care options was computed for each of five basic scenarios for which we assigned charges: self-transport directly to an emergency department, self-transport directly to a physician's office, call an emergency department, call a physician's

office, and call 911. The charge for 911 calls was estimated by taking the sum of the mean charge for the emergency department visit plus the mean charge for ambulance transport. For the two scenarios "call an emergency department" and "call a physician's office," we refined our cost estimates based on our follow-up survey of the providers themselves. When the health care professional indicated that telephone treatment advice alone was an option, we considered this scenario as "free of charge." As a conservative measure, we also considered cost-free those providers stating that no action at all would be taken (no telephone advice and no treatment referral). This estimate assumed that patients or other caregivers would do nothing further should their health care professional give no specific guidance in the face of a possibly toxic exposure. We compared these costs with the mean cost per call incurred by the PCC.

Statistical Analysis

We used the χ^2 statistic to test demographic differences between those interviewed and those lost to follow-up or not selected as interview subjects, to test for differences in categorical responses by type of insurance sponsorship in the PCC caller survey, and to test for differences in the background of triage personnel and responses by type of health care provider setting.

Results

We identified 683 PCC callers meeting entry criteria. Of these, 589 (86%) were successfully surveyed, 32 (5%) declined to participate in the study, and 62 (9%) could not be reached by telephone within 72 hours of the initial poisoning call to the PCC, although they did appear to leave valid telephone numbers. There were 3,828 home-managed PCC cases over the study period from which we sampled. (The majority were ineligible for study because of missing or invalid telephone numbers for callback.) Based on computerized PCC data, study cases were somewhat younger (proportion younger than 5 years, 82%, compared with 78% among nonstudied calls; $P < .05$), and the PCC caller for study cases was more likely to be the mother of the exposed case (73% as compared with 63%; $P < .01$).

The frequencies of alternative treatment scenarios reported by the respondents are presented in Table 1. In total, 464 (79%) respondents cited alternatives to a lack of PCC access that involved another health care professional. Only 125 (21%) respondents identified PCC alternatives that would not have directly involved other health care professionals, based on open-ended questionnaire responses such as "Don't know," "Do nothing," "Give first aid only," or "Call an acquaintance." The most common alternative care scenarios were "Call an emergency department" (29%), "Call a physician or another health care provider" (26%), and "Go directly to an emergency department or private physician's office" (20%). A relatively small number (24 [4%]) of those surveyed stated they would have contacted a 911 emergency response as their initial care alternative if PCC services were unavailable.

We analyzed reported alternative care scenarios by insurance status of the poisoning case (Table 1) and found significant differences. Those with private insurance coverage (either through a health maintenance organization [HMO] or private third-party coverage; n = 429) were compared with those covered by Medi-Cal (California's Medicaid), unknown insurance status, or uninsured altogether (n = 160). The publicly insured or uninsured more frequently cited scenarios involving immediate health care professional evaluations, "Go directly to an emergency department or a private physician's office" or "Call 911" (n = 57 [35%] as compared with n = 87 [20%] among those with private insurance; $P < .01$). Significant differences were noted when the HMO-insured group was compared with the third-party–payer group, with the HMO-insured group more

TABLE 1.—*Frequency of Alternative Options Chosen by Public Callers to the San Francisco Bay Area Regional Poison Control Center Versus Health Insurance Status or Carriers of Poisoned Patients Managed at Home (n = 589)*

	Insurance Status				
*Alternate Care Response**	*HMO, No. (%)†*	*Private (3rd Party), No. (%)†*	*Medi-Cal (Medicaid), No. (%)*	*Other, Dan't Know, None, No. (%)*	*Raw Total, No. (%)*
Call an emergency department (ED)	82 (13.9)	46 (7.8)	19 (3.2)	23 (3.9)	170 (28.8)
Call a physician (MD) or other health care provider	45 (7.6)	90 (15.3)	5 (0.8)	10 (1.7)	150 (25.5)
Go directly to an ED or MD office	41 (7.0)	33 (5.6)	33 (5.6)	13 (2.2)	120 (20.4)
Call 911	7 (1.2)	6 (1.0)	7 (1.2)	4 (0.7)	24 (4.1)
All other responses‡	36 (6.1)	43 (7.3)	17 (2.9)	29 (4.9)	125 (21.2)
Column total	211 (35.8)	218 (37.0)	81 (13.8)	79 (13.4)	589 (100.0)

HMO = health maintenance organization

*Of 429 with health insurance vs 160 without or on Medi-Cal by alternative care response, $P < .0001$, by χ^2 analysis.

†Of 429 with health insurance, HMO vs private third-party–payer group by alternative care response, $P < .0001$, by χ^2 analysis.

‡Breakdown of all other responses included "Don't know" (24), "Do nothing" (23), "Give first aid only" (14), "Call an acquaintance" (14), and miscellaneous (50).

TABLE 2.—*Management Options of Health Care Professionals* for Public Calls Regarding Suspected Poisonings, by Type of Facility*

Option	Response to Public: Hospital Emergency Department (ED), No. (%)	Private Physicion's (MD's) Office, No. (%)	Total, No. (%)
Refer directly to ED or MD's office	11 (29)	33 (43)	44 (39)
Call 911	1 (3)	16 (21)	17 (15)
Give treatment advice over the phone	6 (16)	9 (12)	15 (13)
Not sure of unknown responses	20 (53)	18 (24)	38 (33)
Total	38 (100)	76 (100)	114 (100)

*Responses to question "If the poison control center was not an option, what would you recommend?"
†P = .003 for comparison of management option by emergency department or private office, by χ^2 analysis.

likely to contact an emergency department (n = 82 [39%] as compared with n = 46 [21%] among those with third-party–payer coverage; $P < .01$) when they did cite an alternative provider.

Of the 312 respondents who indicated they would call either an emergency department or a physician, we identified 135 specific health care professional practices (78 physicians' offices and 57 hospital emergency departments). Of these, we successfully surveyed 114 (84%; 76 [97%] of the physicians' offices and 38 [67%] of the hospital emergency departments). No private physician's office was studied in one county where none was identified. Of the health care provider respondents, 88 (77%) indicated that a nonlicensed health care professional (such as a medical clerk) handled all incoming calls from the public. Significant differences were found between hospital emergency departments and private physicians' offices, with the latter more frequently using non-health care professionals to triage public calls (n = 72 [95%] as compared with n = 16 [42%] for hospital emergency departments; $P < .01$).

Of the health care provider respondents, 103 (90%) indicated that their practices had a specific policy for handling a call from the public involving a poisoning. Of the health care provider respondents, 100 (88%) said that their policy was to call the PCC on all poisonings. All 38 (100%) of the hospital emergency departments and 62 (82%) of the private physicians' offices would call the PCC.

Table 2 provides a breakdown by type of health care professional practice for all options cited by health care provider respondents if PCC services were not available. Significant differences were found in response by health care provider settings. A private physician's office more frequently cited "Go directly to an emergency department or a private physician's office" (n = 33 [43%] as compared with n = 11 [29%] among emergency departments) and "Call 911" (n = 16 [21%] as compared with n = 1 [3%]; $P = .003$).

The mean base charges ascertained for an emergency department and private physician's office visit for an asymptomatic child with a suspected poisoning were $170 (range, $107 to $428) and $54 (range, $30 to $125), respectively. The mean charge per ambulance transport was $465 (range, $345 to $596). The mean charge incurred as a result of a 911 call followed by ambulance transport and an emergency department visit was computed as $635.

After integrating the PCC caller and follow-up health care professional survey results and assigning these charge figures to the alternative treatment options, we computed total possible charges of $71,924 for the 589 cases studied. All of these charges derived from only 412 cases (70% of the study respondents) with an alternative treatment option for which a charge was assigned. The total estimated charges for alternative scenarios were $19,040 for those who would go directly to an emergency department and $432 for those who would go directly to a physician's office. The total charges for those who would call either an emergency department, physician's office, or 911 were $10,870, $26,342, and $15,240, respectively.

The comparative cost to handle all 589 survey cases by PCC telephone consultation was $13,547, based on a per-case cost of $23 computed from the PCC total operating budget for fiscal year 1991-1992. Based on these data, the total net cost savings for 33,669 home-managed cases by the PCC for calendar year 1991 was $3.3 million. Figure 1 provides a comparative break-

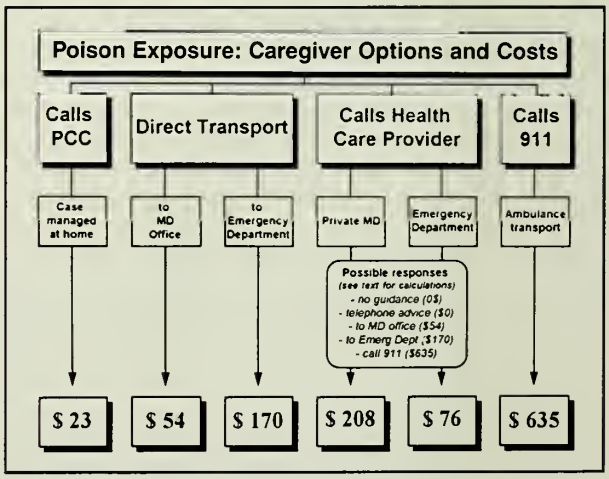

Figure 1.—The diagram shows comparative mean per-case charges for alternative care scenarios cited by poison control center (PCC) callers. All responses to the hypothetical open-ended question "If you could not have reached the poison center when you called after [name of patient] was poisoned, what would you have done?" for which a charge could be ascertained were included. For the mean per-case charges under "Calls Health Care Provider," the charge estimate assumes PCC callers would not take the patient to a health care facility when the health care provider response was "no advice would be given." A "free of charge" was assigned for this scenario or if telephone advice alone was cited by the health care provider. The cost of a 911 response includes transport and emergency department visit.

down of alternative care options taken by the study respondents and the corresponding average per-case charges versus the operating cost per PCC–home-managed case.

Discussion

Our study suggests that poison control centers can greatly reduce the use of other care services, providing a large savings in health care costs. Our findings confirm previous investigations of alternatives to poison control center case management, while providing specific cost and charge data not included in earlier studies.[1-6]

Although we focused on direct cost savings, this is a conservative assessment because it does not include likely indirect benefits of poison center services. For example, one benefit of poison control center services not integrated into our analysis is the effect of timely, expert guidance for assessment and first aid. Without appropriate experience, it is difficult to properly assess risk from a poisoning exposure. Consistent with the public perception of risk, even after nontoxic exposures, 120 (20%) study respondents said that, without access to the poison control center, they would take the exposed person directly to a health care professional. Conversely, we also found that those surveyed would have proceeded with alternative first-aid measures without professional guidance. The likelihood of inappropriate first aid is great, especially given the documented variety of information printed on product labels, some of which recommend first-aid procedures that are more hazardous than the product itself.[9,10]

Another problem-ridden response suggesting a poison control center benefit difficult to quantify is the alternative scenario of no action at all. The "wait and see what happens" approach may result in a delay in proper care for exposures, where toxicity is likely without evaluation and treatment. Even if cases self-refer appropriately, private physicians' offices may be ill-equipped to handle serious medical emergencies.[11]

A lack of poison control center services could create other hardships, albeit without direct health care costs. In particular, parents of young children exposed to possible toxins are likely to experience considerable stress due to uncertainty while on a frantic trip to their local emergency department or private physician's office followed by a likely extended period of waiting for care.

Local emergency response systems are overburdened and under heavy public demand.[12] Although prudent public health care policy aims to reduce unnecessary use of emergency departments and other emergency services,[13,14] our study indicates that a loss of poison control center access would have the opposite effect. This would be further exacerbated by the higher proportion of publicly insured or uninsured in our study who were more likely to proceed directly to an emergency department or to call 911 for emergency assistance.

Our study may be subject to selection bias. The study group, with a somewhat greater proportion of women calling about their exposed child, may react differently to the hypothetical situation we provided than that for the general population of poison control center callers. Reported alternative scenarios may be conservative, however, because those surveyed had the knowledge when surveyed ex post facto that the "poisoning" case indeed did well with simple home management. Another bias may occur in our assessment of the behavior of health care professionals when faced with a hypothetical caller with a toxic exposure. For example, such responses could change over time in a region where access to a poison control center was lost, although this could as easily evolve to more aggressive (and costly) care in the face of medical uncertainty.

Our cost estimates were based on the lowest possible charges incurred from an emergency department or physician's office visit. Again, these were conservative estimates because special monitoring, laboratory procedures, and medication would likely be administered, in some cases augmenting costs. We also conservatively assumed that callers would have done nothing more had their health care professional given no specific telephone guidance in the absence of poison control center services. In all likelihood, a proportion of such callers would self-refer for on-site evaluation despite the lack of a physician's recommendation to do so.

As with most poison control centers nationally, the bulk of funding to the poison control center is local and voluntary. Consistent reductions in poison control center funding have come from its sponsoring hospitals and county, as well as the state general fund. This trend of a loss of governmental and sponsoring hospitals has been mirrored by poison control centers throughout the State of California and nationwide. Four California poison control centers were threatened with closure in fiscal year 1991-1992, with one poison control center in 1992 and one in 1993 actually closing.

In summary, direct public access to poison control center services probably reduces the consumption of emergency health care resources and thereby reduces health care costs. The estimated charges for hypothetical alternative care options if the PCC were not available may exceed the cost for poison control center telephone consultation by a factor of at least five. The loss of poison control center services may have a substantial financial impact on third-party and government-based health insurers alike, adding a major burden to overall health care costs.

Acknowledgment

The contributions of the staff of the San Francisco Bay Area Regional Poison Control Center made this study possible.

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* * *

The Abortion

She came across in the hands of paramedics
who had stuffed her full of packing
and wore her bright blood in their laps.
"Light bulb," their report read,
"self-inflicted." She hissed
straight past the whispering
ER doors to us, the OR—
floor of last resort.

As we unravelled bandages
she went the color of old wax.
Stained shards tinkled to the floor
and clotted to our shoes
as we tried to keep her
(so sharded, so small,
the long ones imbedded in the blooming
bulb of uterus) and though we worked
to get her back, she bled out
on our clean white sheets.

Mitch, who gave the anesthesia,
pumping sweet air and oblivion,
helped me wrap the shroud
and then we dropped our blood-
drenched scrubs and all constraint
at the men's room door and together
in the little shower, we let the water,
hot as we could stand it,
wash over us.

ELLEN DUDLEY©
Marlboro, Vermont

Articles

Underreporting of Fatal Cases to a Regional Poison Control Center

PAUL D. BLANC, MD; THOMAS E. KEARNEY, PharmD;
and KENT R. OLSON, MD, *San Francisco, California*

We assessed fatal drug overdose and poisoning case surveillance by a regional poison control center, comparing it with medical examiner determinations of death by poisoning over the same 2-year period and from the same catchment area. We studied 358 fatal cases of poisoning or drug overdose reported by a medical examiner and 10 fatal cases of poisoning or drug overdose reported by a poison control center, analyzing demographics and other case-associated factors with possible successful poison control center case surveillance. Of the medical examiner cases, 245 (68%) were prehospital deaths. Of the remaining 113 emergency department or hospital cases, only 5 (4.4%) were also reported to the poison control center. Compared with cases involving illicit drugs, other narcotics, and sedative drugs, those that involved other prescription drugs (relative odds, 30.6; 95% confidence interval, 2.7 to 351) and over-the-counter products and other substances (odds ratio, 18.9; 95% confidence interval, 1.4 to 257) were significantly more likely to be reported to the poison control center. Most fatal cases of poisoning and drug overdose are not detected through poison control center surveillance. For prevention and treatment, health planners and policy makers should recognize the implications of case underreporting.

Blanc PD, Kearney TE, Olson KR: Underreporting of fatal cases to a regional poison control center. West J Med 1995; 162:505-509)

Poisoning and drug overdose is a leading cause of injury deaths. A recent report on injury-related morbidity in San Francisco, California, identified poisoning and overdose as the single greatest cause of fatal injuries in that county.[1] The direct and indirect economic costs of poisoning are staggering, estimated to be greater than $8 billion annually nationwide.[2(p50)]

Over recent years, a network of poison control centers in the United States has provided an important and widely cited source of incidence data for poisoning and drug overdose through the American Association of Poison Control Centers.[3]* There is, however, a paucity of other reliable epidemiologic data on poisoning and drug overdose. For this reason, little is known about cases that never reach poison control center consultation. For example, we recently found that among 533 cases of poisoning and drug overdose presenting to an emergency department, fewer than 1 in 4 were reported to the regional poison control center that directly served the reporting hospitals.[4] Reporting rates may be even poorer from sites more remote from a regional poison control center. Moreover, there were few deaths in our previous emergency department series, which makes those findings difficult to extrapolate to the reporting of cases of fatal poisoning.

We analyzed a series of fatalities that were determined by a medical examiner's investigation to be causally related to poisoning or drug overdose and compared them with deaths reported by a poison control center in the same jurisdiction. Our goal was to determine the proportion of medical examiner cases that would also appear in poison control center reporting. We also wished to identify factors that are associated with a more successful poison control center case surveillance.

Cases and Methods

We studied all fatalities investigated by the San Francisco City and County Medical Examiner's office in which poisoning and drug overdose was attributed to be the principal cause of death. We also studied all cases with a fatal outcome over a matching time period in the same geographic jurisdiction reported to the San Francisco Bay Area Regional Poison Control Center (PCC). The study was carried out retrospectively and covered a two-year period between July 1, 1988, and June 30, 1990. We identified eligible cases from a computerized database listing all cases during that time period for the med-

*See also the editorial by Toby Litovitz, MD, "Listen, Ye Legislators, Our Children Need You!" on pages 552-553 of this issue.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
OR = relative odds (odds ratio)
PCC = San Francisco Bay Area Regional Poison Control Center

ical examiner and from a file of all fatal cases maintained by the PCC.

The medical examiner's determination of death is carried out only after a detailed case investigation. In cases where poisoning or drug overdose is suspected, the investigation routinely includes toxicologic testing of blood and other tissue specimens using gas chromatography and mass spectroscopy. A core panel of substances tested includes barbiturates (amobarbital, phenobarbital, secobarbital), benzodiazepines (chlordiazepoxide, diazepam, nordiazepam), amphetamine and methamphetamine, antihistamines, phencyclidine, cocaine and benzoylecgonine, narcotics and opiates (methadone, morphine, codeine, propoxyphene, norpropoxyphene), antidepressants (fluoxetine, clomipramine, doxepin, amitriptyline, nortriptyline, imipramine, desipramine), phenothiazines, salicylate, and phenytoin. In addition, other specific toxins may be evaluated according to the clinical history.

We extracted from the case record the final medical examiner assessment of the specific drug or toxin responsible for the poisoning death or whether the case was attributed to "polydrug" overdose. The medical examiner's attribution of cause of death frequently does not identify a single toxin as the primary cause of death in fatal overdoses that involve several drugs. We also extracted from the medical examiner case record the identification and number of different toxins found in toxicologic testing. We categorized toxins into one of the following three broad groups:

- Illicit drugs, narcotics, or sedative-hypnotic drugs with abuse potential—including cocaine, amphetamines, heroin or other narcotics, benzodiazepines, and barbiturates;
- Other prescription medications—such as antidepressants, theophylline, or digoxin; and
- Over-the-counter medications and other toxins—including aspirin, acetaminophen, and carbon monoxide.

The categories were not mutually exclusive as toxicologic testing could identify substances from more than one broad category. We did not analyze medical examiner toxicologic data on ethanol detection among these cases.

In addition to the medical examiner's attribution of cause of death and toxicologic data, we also extracted from the medical examiner case record demographics, location of death (prehospital, emergency department, or hospital inpatient), and attribution of intention (suicide, nonintentional, or intentionality unknown).

From the PCC file of fatal cases, we extracted demographics, toxicity data, and the PCC determination of whether the death was related to the reported exposure. This determination was made by the PCC in connection with data reporting to the American Association of Poison Control Centers and is not dependent on the medical examiner's case reporting.

We analyzed the data employing a standard computerized statistical package (SAS Institute, Cary, North Carolina). We tested the differences in case characteristics by location of death using the χ^2, Fisher's exact test, or, for the continuous variable of age, by analysis of variance. Excluding prehospital deaths, we analyzed factors associated with case reporting to the PCC, calculating the relative odds or odds ratio (OR) and 95% confidence intervals (95% CI) about those estimates. This was a bivariate analysis, except for toxin type, where we estimated the OR including prescription medications and other products in the same model.

Results

We identified 358 medical examiner cases of drug or toxin-attributed fatalities over the 24-month study period (Table 1). Of these, 245 (68%) were prehospital cases in which the victim was found dead and was not brought for evaluation to a hospital emergency department. Demographically, the study group was largely male (78%), with a mean age of 39 years.

As shown in Table 1, the substances most frequently involved were illicit drugs, narcotics, or sedative-hypnotics, identified by toxicologic testing in 317 (89%) cases. Of the 317 cases involving such drugs, the medical examiner attributed the primary cause of death to a single toxin in the following distribution: heroin, 97 (31%); cocaine, 53 (17%); amphetamines, 14 (4%); codeine or derivatives, 7 (2%); and benzodiazepines and barbiturates, 4 (1%) each. Deaths from other prescription medications, over-the-counter products, and other substances where the cause was attributed to a single toxin included 11 due to cyclic antidepressants, 7 due to carbon monoxide exposures, and 1 each attributed to acetaminophen, salicylate, digoxin, and theophylline. Among all deaths, cyclic antidepressants were identified by toxicologic testing as present in 43 (12%) of the cases.

When analyzed by site of death, cases differed significantly by three locations: prehospital victims found dead and not taken to an emergency department, those declared dead on arrival or dying in an emergency department, or victims surviving at least until hospital inpatient admission (Table 1). The proportion of fatalities determined by the medical examiner to be due to suicide (as opposed to nonintentional or of undetermined intent) differed significantly by site of death, being most common among those admitted to a hospital (9 [25%] of 36 cases) and least common among emergency department deaths (4 [5%] of 77 cases). The proportion of drug-related fatalities where illicit drugs, other narcotics, or sedative-hypnotics were detected toxicologically also differed significantly by site of death, being most common among the emergency department cases. In contrast, deaths involving other prescription medications were significantly less frequent for the emergency department location. The median length of stay until death among the 36 cases

TABLE 1.—*Medical Examiner Drug- and Toxin-Attributed Cases Over 24 Months by Site of Death*

Case Variables	Site of Death: Prehospital (n = 245)	Emergency Dept (n = 77)	Hospital (n = 36)	All Cases (n = 358)
Age, years, mean ± SD	39 ± 11	39 ± 10	40 ± 13	39 ± 11
Sex, male, No. (%)	198 (81)	57 (74)	24 (67)	279 (78)
Nonwhite or Hispanic, No. (%)*	75 (31)	34 (44)	16 (44)	125 (35)
Suicidal intent, No. (%)*	42 (17)	4 (5)	9 (25)	55 (15)
Drug or toxin types, No. (%)†				
Illicit drugs, narcotics, sedatives*	217 (89)	74 (96)	26 (72)	317 (88)
Other prescription medications*	43 (17)	3 (4)	8 (22)	54 (15)
Over-the-counter and other substances	29 (12)	5 (6)	4 (11)	38 (11)
Multiple drugs or toxins identified	97 (40)	26 (34)	16 (44)	139 (39)

SD = standard deviation

*$P < .05$, differences by site of death.
†Multiple categories of drug or toxin type are possible.

admitted to a hospital was 3.5 days (interquartile 25% to 75% range, 1 to 5 days).

Over the same 24-month study period, 15 fatal case consultations were reported to the PCC that were geographically under the jurisdiction of the San Francisco medical examiner (approximately 15% of all deaths reported to this PCC). We excluded five cases from further analysis. These were cases for which the PCC consultation concluded that the death was unrelated to drug or chemical exposure. Among these five excluded unrelated deaths, the medical examiner's office had either "cleared" the case on initial reporting (n = 2) or had no record of the case (n = 3).

The remaining ten cases are listed in Table 2. For five cases, there was concurrence between the assessment of the PCC and the medical examiner. In one case in which the medical examiner attributed the cause of death to theophylline overdose, the PCC assessment was that of an unrelated fatality. In two cases of PCC assessment of drug-attributed death, the medical examiner's conclusion was that of an unrelated cause of death. The two other PCC cases had been "released" by the medical examiner and therefore were not evaluated further. These discordant cases, which are detailed in Table 2, are heterogeneous in relation to both exposure and intent.

Altogether, 6 (1.7%) of 358 medical examiner cases were reported to the PCC. These 6 included only 1 (0.4%) of the 245 prehospital deaths compared with 5 (4.4%) of the 113 emergency department or hospital fatalities ($P = .01$). We further studied factors associated with PCC reporting of deaths that were also attributed by the medical examiner to be toxin-related, limiting analysis to the 113 emergency department or hospitalized fatalities (Table 3). Of these medical examiner cases, 5 (4%) also involved PCC consultations. Of the 36 cases admitted to a hospital, 4 (11%) were reported to the poison control center. Survival until hospital admission as compared with emergency department death was strongly associated with PCC consultation (OR = 9.5; 95% CI, 1.02 to 88). Among those admitted, length of stay was unrelated to PCC consultation (OR = 1.1 per 5 days of stay). Suicidal intent as compared with unintentional or undetermined intentionality was also strongly associated with PCC consultation, demonstrating an OR of 14.7 (95% CI, 2.2 to 99).

Cases involving prescription medications other than narcotics, benzodiazepines, or barbiturates (OR = 31) and cases involving over-the-counter products or other substances (OR = 19) were significantly more likely to have been reported to the PCC. Nonetheless, even among the 13 deaths among emergency department or hospitalized cases where no illicit drugs, narcotics, or sedative-hypnotics were detected, only 3 (23%) were indeed reported to the poison control center. Cases in which multiple drugs or toxins were detected were no more likely to have been reported to the poison control center.

Discussion

We found that poison control center reporting is far less comprehensive than medical examiner case detection of fatal poisoning and drug overdose. Even when the analysis is limited to cases presenting to emergency departments or admitted to a hospital, only 1 in 20 medical examiner-reported poisonings had also led to a poison control consultation. Among those surviving until hospital admission, the poison control consultation rate increased to 11%. Poison control center surveillance was disproportionately weighted toward suicides and to cases that did not involve illicit drugs or other narcotics or sedatives.

Two recent studies from the northeastern United States have also compared medical examiner- and poison control center-reported cases. A retrospective study of a two-year incidence of poisoning deaths in the State of Massachusetts (1986 to 1987) compared medical examiner and poison control center reporting after excluding prehospital deaths (which accounted for 77% of their cases).[5] Of 95 medical examiner-reported cases, 49 (52%) had also been reported through the poison control center system. That study also analyzed death certificates, a source that we did not examine in our study. It is interesting to note that of 43 death certificate-identified poisoning deaths that were not medical examiner cases, only 3

TABLE 2.—*Drug-Related Fatalities in San Francisco City and County Reported to the San Francisco Bay Area Regional Poison Control Center (PCC) Over 24 Months**

Case	Drug	Site of Death	Intention	Age, yr	Gender	ME Report	PCC Report
1	Acetaminophen, codeine, ibuprofen	Hospital	Suicide	85	Female	Related	Related
2	Trichloroethane	Prehospital	Suicide	47	Male	Related	Related
3	Maprotiline, dextromethorphan	ED	Suicide	17	Female	Related	Related
4	Theophylline	Hospital	Unintended	77	Male	Related	Unrelated
5	Amitriptyline	Hospital	Suicide	25	Female	Related	Related
6	Heroin, cocaine	Hospital	Unintended	37	Male	Related	Related
7	Colchicine	Hospital	Unintended	70	Male	Unrelated	Related
8	Amphetamine	Hospital	Unintended	51	Male	Unrelated	Related
9	Procainamide	Hospital	Unintended	83	Male	NA	Related
10	Aspirin	Hospital	Unintended	61	Female	NA	Related

ED = emergency department, ME = medical examiner, NA = not ME-investigated case

*Not included: Five PCC case consultations over study period for deaths assessed as unrelated to exposure. Two of these were ME cases also determined to be unrelated. Three others were not ME-investigated.

(7%) were also reported through a poison control center. Moreover, 25 additional cases in that series were detected solely through poison control center surveillance. In comparison, our PCC series identified 4 of 9 cases (excluding 1 prehospital death) as poisoning-related deaths in which the medical examiner either did not concur or had not evaluated the case.

Another retrospective study of a four-year incidence of fatal poisoning and drug overdose in Rhode Island (1986 to 1989) identified 230 (62%) prehospital deaths among 369 studied.[6] Of 139 non–prehospital cases, 33 (24%) were also reported to the regional poison control center. There were 8 other poison-related deaths reported to the poison control center that did not appear as medical examiner-reported poisoning cases.

Important differences and similarities exist between our study and these other series. Most striking are differences in the incidence of medical examiner-reported poisonings, as shown in Table 4.[5-7] These data are based on crude rates, unadjusted for age or other demographic variables, but comparable in the exclusion of prehospital cases. In contrast to the differences in medical examiner-derived incidence data, PCC-based poisoning fatality rates are similar among the three locations, reflecting the counterbalancing effect of varying PCC and medical examiner case overlap. All of the studies employed similar retrospective designs in states with comparable medical examiner reporting requirements and with regional poison control centers meeting the same national American Association of Poison Control Center performance standards. Based on our data, we cannot assess whether the observed differences in medical examiner incidence reflect a true higher incidence of poisoning deaths in San Francisco or, alternatively, whether more complete medical examiner investigations occur in that area.

Other important differences exist in the study populations. The leading specific toxin cause of death in each of the other two series was carbon monoxide, which was relatively uncommon among our cases, where drugs of abuse predominated. In addition to regional differences with the northeastern United States, our study catchment area was entirely urban rather than a statewide rural-urban mix. Of note, an important shortcoming shared by our study and the previous investigations is a relative lack of pediatric fatalities, a group for which poison control reporting may indeed be effective compared with medical examiner surveillance. The ability to generalize our data is tempered by all of these geographic and case-mix considerations.

Although the number of cases we analyzed after excluding prehospital deaths was similar to that in these studies, the small number of cases reported to the PCC limits our ability to identify other than strong statistical associations such as those we observed for drug type or

TABLE 3.—*Factors Associated With Report of Poisonings to a Regional Poison Control Center (PCC) for 5 Among 113 Non–Prehospital Medical Examiner (ME) Cases*

	PCC Reporting*	
Factors Studied	Relative Odds	95% CI
Age ≤ 35 yr	2.7	0.4-17
Sex, female	4.1	0.7-26
White, non–Hispanic	3.3	0.4-31
Survival to hospital admission	9.5	1.02-88
Suicidal intent	14.7	2.2-99
Multiple drugs or toxins identified	0.4	0.04-3.8
Substances identified by toxicology testing		
Illicit drugs, narcotics, sedatives (referent)	1.0	--
Other prescription medications	30.6	2.7-351
Over-the-counter substances or other	18.9	1.4-257

CI = confidence interval

*All analyses are bivariate except for "substances identified," which included the categories "other prescription medications" and "over-the-counter substances or other" as 2 predictors in a multiple logistic regression.

TABLE 4.—*Medical Examiner (ME) and Poison Control Center (PCC) Poisoning Incidence Excluding Prehospital Deaths: Current Study Compared With Previously Published Data**

Incidence Measures, %	Study Locations† San Francisco City and County	Rhode Island Statewide	Massachusetts Statewide
ME annual cases/ 10^5 catchment population	7.5	3.6	0.8
ME annual cases/ 10^3 deaths, all causes	7.1	3.7	0.9
ME annual cases/ 10^3 hospital beds	9.2	6.4	1.2
Annual PCC deaths/ 10^5 catchment population	0.6	1.1	0.7
ME cases reported by PCC, %	4.0	24.0	52.0
PCC cases reported by ME, %	56.0	80.0	64.0

*From US Census Bureau[7]; catchment population data current for 1986, total number of deaths for 1984, and total number of hospital beds for 1985. No age or sex adjustments have been made.

†San Francisco locations comprise current study, 1988 to 1990; Rhode Island study period, 1986 to 1989 (Linakis and Frederick[6]); and Massachusetts study period, 1986 to 1987 (Soslow and Woolf[5]).

suicidal intention. For example, although among fatalities female cases were more than four times more likely to be reported to the PCC, our 95% confidence intervals about this estimate were wide and did not exclude unity. The small number of PCC-reported medical examiner cases also precluded multivariate analysis or stratification that could address the potential relationship between demographics, intention, and toxic substances identified. Moreover, as shown in Table 1, the association between both suicidal intent and certain toxin types on the one hand and PCC case reports on the other may be confounded by survival to hospital admission. These statistical limitations should be kept in mind when interpreting our findings.

Our study confirms and amplifies the principal finding of other studies: fatal poisonings frequently do not receive poison control center evaluation and consultation. The implication is twofold. Among those surviving to receive medical care, reducing morbidity and mortality is the focus of PCC consultation. This can be viewed as a secondary prevention goal. Among the 113 cases reaching emergency departments (of whom 36 survived to hospital admission), 96% did not receive the possible benefit of PCC consultation. It is generally accepted that poison control consultation leads to improved outcome, particularly when regional as opposed to local centers are used.[8] Our findings suggest that poison control centers may need to improve awareness among health professionals of the possible benefits of such consultation. Even though we found that PCC reporting was marginally more frequent, after excluding prehospital deaths, the type of cases reported appear heavily skewed by toxin type and suicidal intent and likely reflect demographic biases as well. This being said, it must be emphasized that our data demonstrate that most poisoning and drug overdose deaths occur before the victims reach medical care. For prehospital deaths, primary rather than secondary prevention strategies are paramount. The principal role of poison control centers in primary prevention is in public education. They clearly have a narrow role "postmortem," although consultations are sometimes sought to clarify clinicopathologic correlations. Nonetheless, poison control centers are likely to remain an ineffective tool for the passive collection of surveillance data on such prehospital deaths.

It is crucial to recognize the shortcomings in poison control center fatality reporting. These shortcomings highlight the critical need for improved primary prevention of those cases of overdose that never survive to receive medical intervention and for improved secondary prevention through poison control case consultation for those patients who do receive physician treatment.

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Tremor Disorders
Diagnosis and Management

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Tremor is commonly encountered in medical practice, but can be difficult to diagnose and manage. It is an involuntary rhythmic oscillation of a body part produced by reciprocally innervated antagonist muscles. Tremors vary in frequency and amplitude and are influenced by physiologic and psychological factors and drugs. Categorization is based on position, posture, and the movement necessary to elicit the tremor. A resting tremor occurs when the body part is in repose. A postural tremor occurs with maintained posture and kinetic tremor with movement. Various pathologic conditions are associated with tremors. Essential tremor, which is the most common, is postural and kinetic, with a frequency between 4 and 8 Hz, and involves mainly the upper extremities and head. Essential tremor responds to treatment with primidone, β-blockers, and benzodiazepines. Parkinson's disease causes a 4- to 6-Hz resting tremor in the arms and legs that responds to the use of anticholinergics and a combination of carbidopa and levodopa. Tremor can also be a manifestation of Wilson's disease, lesions of the cerebellum and midbrain, peripheral neuropathy, trauma, alcohol, and conversion disorders. Treatment should be directed to the underlying condition. Stereotactic thalamotomy or thalamic stimulation is a last resort.

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Tremor is an involuntary, rhythmic, oscillatory movement produced by reciprocally innervated antagonist muscles. It is commonly seen in general medical practice, and the diagnosis can be challenging to clinicians. Therapy for the many types of tremor depends on making the correct diagnosis. We review the different categories of tremor, their clinical presentation, and current treatment modalities.

Classification

There are two classification systems used in evaluating tremor.[1] The first is based on whether tremor occurs at rest (resting tremor) or with action (Table 1). Tremors with movement (action) are subdivided into postural tremor, which occurs with maintained posture; kinetic or intention tremor, which occurs with movement from point to point; and task-specific tremor, occurring only when doing highly skilled activity. A postural tremor is tested by having a patient hold the arms stretched out in front. Kinetic or intention tremor is tested by the finger-to-nose maneuver.

The second tremor classification is by cause. Tremor can be due to a variety of conditions, both physiologic and pathologic (Tables 2, 3, and 4).

Physiologic Tremor

Physiologic tremor occurs normally when attempting to maintain posture. The frequency is 8 to 12 Hz in the hands, but may be as slow as 6.5 Hz in other body parts.[2] The frequency decreases with age, especially after the fifth decade. Under certain circumstances and with drugs, it can increase and become symptomatic (Table 2). Conditions such as emotional stress and exercise can enhance physiologic tremor. Drugs such as amphetamines, certain anticonvulsants, and antidepressants also may exacerbate the tremor (Table 3). The best therapy is to remove the cause, but if that is not possible, then trying a β-adrenergic antagonist such as propranolol hydrochloride might be helpful.

Tremor can occur in a variety of pathologic conditions (Table 4). The more common ones will be discussed.

Essential Tremor

Essential tremor is the most common movement disorder It is estimated to affect in excess of 1 million persons in the United States.[3] There is no sex or racial difference, and it often occurs in families as an autosomal dominant trait. Its onset is insidious with varying progression over time. It may appear in childhood or adult

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TABLE 1.—*Tremor Classification*

Tremor Type	*Occurrence*
Resting	When limb is fully supported against gravity and the muscles are not voluntarily activated
Postural	When limb is positioned against gravity
Kinetic	During any type of movement
Intention	Exacerbated toward the end of goal-directed movement
Task-specific	Only during performance of highly skilled activities such as writing or playing music

life, and it slowly progresses with age. The frequency is usually between 4 and 8 Hz. It is most evident with hands held in posture and attenuates during voluntary movement. In some patients, however, the tremor is most severe with movement. At times, when severe, it may persist at rest, making the distinction from Parkinson's disease difficult.

The hands are most affected, but other body parts may also be involved. Head tremor, commonly associated with hand tremor, may occur in isolation and may show a different pharmacologic response from hand tremor. Speech involvement (voice tremor) can result from tremor of the muscles of phonation or respiration or of the head and neck.

Variants of essential tremor include primary writing tremor, in which writing elicits a pronation-supination tremor not seen in other arm movements, and orthostatic tremor, which is present in the lower limbs during standing and may disappear with sitting or walking.[3,4] Essential tremor may be associated with other movement disorders, including cervical dystonia, writer's cramp, and spasmodic dysphonia.[5,6]

Although a postural tremor similar to essential tremor occurs in Parkinson's disease, patients with this tremor are not predisposed to Parkinson's disease.[7] Essential tremor lessens temporarily with the ingestion of alcohol, an effect that lasts from 30 minutes to several hours and is an important distinguishing feature. A number of external factors such as emotion and stress exacerbate the severity of essential tremor. Although this condition does not shorten the life span, quality of life may be greatly affected.

TABLE 2.—*Factors That Exacerbate Physiologic Tremor*

Emotions—anxiety, stress, fear
Exercise, fatigue
Alcohol withdrawal
Hypoglycemia
Thyrotoxicosis
Pheochromocytoma
Drugs

TABLE 3.—*Drugs That Exacerbate or Induce Tremor*

Drug Class	*Examples*
β-Adrenergic agonists	Theophylline Metaproterenol sulfate Terbutaline sulfate
Amphetamines	
Anticonvulsants	Valproate sodium
Lithium carbonate	
Neuroleptics	
Tricyclic antidepressants	
Methylxanthine	Caffeine Theophylline
Dopamine agonists	
Heavy metals	Mercury (hatter's shakes) Lead Arsenic
Alcohol	

Treatment

Medical treatment may not be necessary when essential tremor causes no disability. β-Adrenergic–receptor antagonists are the drugs of first choice. Propranolol hydrochloride in daily doses of 80 to 320 mg is given most often.[3] Long-acting propranolol is also effective.

Metoprolol, because of its cardioselectivity, is useful when asthma is present. Nadolol can be effective and has fewer central nervous system side effects.[2] Primidone, an anticonvulsant, has shown a degree of therapeutic response comparable to that of propranolol.[8] In doses of 50 to 250 mg at nighttime, it can markedly reduce tremor. About 20% of patients have an acute idiosyncratic reaction in the form of dizziness, headache, ataxia, nausea, and vomiting.[9] This reaction typically resolves in two to three days and is not a reason to discontinue the medication. The drug regimen should be commenced in small doses, and the patient should be warned of this possible side effect. If the tremor is not controlled with one drug, a combination of primidone and propranolol can be helpful. If tremor is severely disabling and unresponsive to drugs, stereotactic thalamotomy or thalamic stimulation should be considered.[10,11] Sedatives and tranquilizers are rarely effective, although some patients may respond to the use of alprazolam. Clonazepam is, however, the drug of choice in orthostatic tremor.

Tremor of Parkinson's Disease

Parkinson's disease has the symptom complex of tremor, rigidity, bradykinesia, and postural instability. Histologically, there is degeneration of the substantia nigra, and Lewy bodies are present.

Parkinson's disease is neurochemically defined by a dopamine deficiency in the striatum.[9,12] Approximately half of patients with Parkinson's disease present with

TABLE 4.—*Causes of Pathologic Tremor*

- Parkinson's disease
- Other parkinsonian syndromes
- Wilson's disease
- Essential tremor
- Peripheral neuropathy
  - Charcot-Marie-Tooth disease
  - Other hereditary sensorimotor neuropathies
  - Diabetes mellitus
  - Porphyria
  - Demyelinating disease
  - Other
- Cerebellar and midbrain disease
  - Multiple sclerosis
  - Trauma
  - Tumor
  - Other
- Idiopathic dystonia, including focal dystonia
- Psychogenic
- Drugs

tremor; however, 10% never have a tremor.[9] The classic tremor is a resting one, but a postural tremor that is similar to essential tremor can occur and may respond to the use of β-adrenergic blockers. The resting tremor consists of adduction-abduction of the fingers and hands. Flexion-extension of fingers in coordination with adduction-abduction of the thumb gives the classic "pill rolling" tremor. Resting tremor can affect also the legs, jaw, and lips. The frequency is 4 to 6 Hz, and the tremor occurs mainly distally. It dampens when hands are in motion and is asymmetrical at least initially. Emotional stress in particular increases the amplitude. The mainstay of the treatment of Parkinson's disease is a combination of carbidopa and levodopa. The effect on the tremor is variable, and some people may have a poor response. Anticholinergics such as trihexyphenidyl hydrochloride and benztropine mesylate can be useful, but are poorly tolerated especially by older patients.[9,12] Propranolol can be used as adjuvant treatment in doses similar to those used for essential tremor. Stereotactic thalamotomy or high-frequency stimulation of the thalamus directed to the nucleus ventralis intermedius should be considered.

Tremor With Other Basal Ganglia Diseases

Tremor can be a component of the symptom complex in patients with dystonic disorders, such as spasmodic torticollis.[5] The administration of botulinum toxin is effective for focal dystonia. Treatment of the underlying condition may also ameliorate the tremor. In Wilson's disease, tremor can be the presenting symptom. It can occur with postural and kinetic movements and is most prominent in the proximal muscles. At the shoulders it is described as "wing-beating" tremor. The treatment of Wilson's disease with penicillamine may ameliorate the tremor.[2]

Cerebellar Tremor

Patients with cerebellar disease have both postural and kinetic tremors. Various types of postural tremors have been described. The most common consist of oscillations of the arms about the shoulders or of the legs about the hips.[2] It is referred to as titubation when it affects the trunk and head. There is also a mild postural tremor that is more rapid (frequency of 10 Hz) with distal predominance. The characteristic cerebellar kinetic tremor has a frequency of 3 to 5 Hz. It is evident on finger-to-nose and heel-to-shin tests. It appears at the initiation and along the course of a movement and has a coarse side-to-side component. The amplitude of the tremor increases as the limb is extended or on approaching a target. The most common cause of cerebellar tremors is multiple sclerosis, but brain-stem tumors or strokes and degenerative and paraneoplastic diseases can also be responsible. Cerebellar tremors are thought to be due to lesions of the lateral cerebellar nuclei or superior cerebellar peduncle. Lesions of the midbrain around the red nucleus will produce a wing-beating type of tremor. Midline cerebellar disease (lesions in the vermis) will cause bilateral arm tremor and, more commonly, head and trunk tremor (titubation). No effective treatment exists for cerebellar tremors.

Tremor With Peripheral Neuropathy

Tremor is a rare manifestation of peripheral neuropathy. It is observed in some patients with idiopathic, demyelinating, hereditary motor and sensory and immunoglobulin M paraproteinemic neuropathies, and, less often, diabetes mellitus, uremia, diseases of anterior horn cells, and porphyria.[1] The tremor is similar clinically to essential tremor. Symptomatic treatment with propranolol, primidone, benzodiazepines, or baclofen is worth attempting. Treatment should be focused on the underlying neuropathy.

Posttraumatic Tremor

Tremor is well known as a consequence of head trauma and appears within a few months after the injury. The frequency is 4 to 6 Hz. It is typically proximal and made worse with movement.[13,14] These tremors may respond to the use of propranolol or stereotactic thalamotomy.[15]

Alcohol Withdrawal Tremor

Tremor is a symptom of alcohol withdrawal. It may occur after a period of relative or absolute abstinence. The earliest and most common withdrawal symptom is a generalized tremor, which has the characteristic of an enhanced physiologic tremor.[16] A more permanent postural tremor can sometimes occur in persons with chronic alcoholism even with alcohol abstinence.

Psychogenic Tremor

Tremor can be a manifestation of hysteria and occurs in young and old people alike. A patient commonly presents with complex tremors (combination of resting, pos-

tural, and kinetic). The history reveals an unusual temporal profile (abrupt onset with variable course), an absence of other neurologic symptoms, selective disability with the ability to perform some functions in the presence of severe tremor, and unusual handwriting. Some patients have a psychiatric history of multiple undiagnosed somatizations. If the affected limb is restrained, the tremor may move to another body part. Diagnosis is difficult, but an important clue is that it disappears when the patient's attention is distracted. Treatment of the underlying psychiatric problem may result in a disappearance of the tremor, but the prognosis is often poor.

Conclusion

Evaluating tremors can be straightforward and challenging at the same time. It is helpful to know if the tremor occurs at rest, with movement, or with a specific task. A history of tremors or movement disorder in the family and pharmacologic exposure can be important. Treatment is available but complicated by drug intolerance and a variable response.

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Articles

Neighborhood-Based Tobacco Advertising Targeting Adolescents

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Based on a paper presented at the annual meeting of the Western Society for Pediatric Research, Carmel, California, February 1994.

Adolescent tobacco use remains a serious problem, and adolescents may be particularly receptive to the glamorous images tobacco companies use in advertisements. A relatively new form of neighborhood-based outdoor advertising, the illuminated bus-stop-shelter billboard, was studied to determine tobacco companies' use of this medium. We hypothesized that in 2 distinct San Francisco, California, neighborhoods, 1 predominantly white and the other mostly Latino, we would find a predominance of tobacco advertising on these billboards in both neighborhoods, that tobacco advertisements would be more prevalent in the minority Latino neighborhood, and that tobacco advertising would target adolescents in both neighborhoods. Each bus-stop-shelter billboard advertisement in the study areas from April 1992 to March 1993 was recorded. The type and frequency of products advertised and qualitative content of tobacco advertisements were analyzed. Adolescents' possible exposure to these advertisements was noted. Our main outcome measures were the percentage of tobacco advertising, possible adolescent exposure to this advertising, and themes of the tobacco advertisements. About 10% of all bus-stop-shelter billboard advertisements in each area promoted tobacco use. Possible exposures to these advertisements were greater in the Latino neighborhood because of a greater adolescent population. Qualitative analyses of tobacco advertisements suggested that adolescents are the primary targets. We urge physicians and educators to explicitly address this form of tobacco advertising, and we urge a ban on neighborhood-based tobacco advertising.

(Ammerman SD, Nolden M: Neighborhood-based tobacco advertising targeting adolescents. West J Med 1995; 162:514-518)

Tobacco use by adolescents is a serious problem, with more than 3,000 teenagers becoming regular smokers each day in the United States.[1] About 50% of smokers start before the age of 18 years, 70% of all students in grades 9 to 12 have tried cigarettes, and about 13% of high school students report frequent cigarette use.[1] According to the Centers for Disease Control and Prevention, cigarette smoking is the most important preventable cause of death in the United States.[2]

Media advertising of tobacco products influences adolescents' decisions to use tobacco,[2-11] with advertising campaigns increasingly targeting youth, women, and minorities.[5,12-19] The Centers for Disease Control and Prevention reports that the three most commonly purchased brands of cigarettes among adolescent smokers (86% of the total) were the three most heavily advertised brands in 1993; only 35% of adults smoke the same three brands.[20] Through various media, adolescents are constantly exposed to the messages promoted by these advertisers. These messages virtually ignore health care concerns and use themes correlated with psychosocial factors that appeal to young people.[21,22] In the messages, the use of these products is associated with healthy activities involving adventure and recreation, independence and sexual attractiveness, professional success, confidence in social settings, and, for young women, weight control and maintaining a thin appearance.[4,12,23-28]

Adolescents may be particularly receptive to the messages of the tobacco companies, as one of the developmental tasks of adolescence is identity formation, which involves, in part, looking for role models beyond the family unit.[29-31] In addition, risk-taking behaviors, including tobacco use, commonly start in middle adolescence.

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Outdoor billboards are a form of advertising that reaches a wide audience; cigarettes are the most heavily advertised product in the outdoor (billboard) media.[4] Three types of billboards are in use throughout the United States: large ones located along freeways, small billboards found adjacent to large city thoroughfares, and shelter posters located in bus-stop shelters along public transportation lines. Previous studies have shown that tobacco advertising is the most prevalent type across all large and small billboard advertising of products and services.[32,33(pp4,5,31)] Tobacco companies using these billboards have broadly targeted ethnic and racial groups and low-income, minority neighborhoods.[34,35]

No study to date has focused on bus-stop-shelter billboards, a relatively new form of advertising currently used in many cities throughout the United States. Bus-stop-shelter billboards are visual advertisements contained in a bus-stop shelter; in San Francisco they are 117 by 170 cm (46 by 67 in). These billboards target neighborhood users of public transportation for school, work, and recreation. They are illuminated to provide 24-hour advertising of a product. The San Francisco Municipal Railway leases the space to a company that maintains the bus-stop shelter and that leases the billboard space to various advertisers on a monthly basis. The bus-stop shelters provide seats and protection from the weather for persons waiting for buses.

People who rely on public transportation or those whose neighborhood school or work are in the vicinity of these bus-stop-shelter billboards are continuously exposed to this form of outdoor advertising because it cannot be turned on or off like television advertising or skipped over like advertising in magazines or newspapers. Even casual observers cannot distance themselves from the intended effects of the advertisement (G. Savin, "Can They Persuade You?" *ETC Etcetera* 1989; 46:177-179).

In San Francisco, these bus-stop-shelter billboards are permitted in areas designated as "neighborhood commercial districts," legally zoned entities defined by the San Francisco Department of City and County Planning. The neighborhood commercial districts contain a combination of commercial and residential uses within or close to residential areas. Because they are neighborhood-based, the advertising on the bus-stop-shelter billboards targets the neighborhood population. The neighborhoods themselves have neither formal political nor legal boundaries, but have generally recognized borders based on census data and definitions from the San Francisco Real Estate Board, and this information is used in designating a neighborhood commercial district. We therefore decided to compare the bus-stop-shelter advertising in two distinct neighborhood commercial districts. One, the Eureka Valley District, has a predominantly white population with a notably higher socioeconomic status and includes the Noe Valley and the Castro neighborhoods. Eureka Valley also has a fairly large gay and lesbian community, although no census data exist on their proportion in the population. The other neighborhood commercial district, the Mission District, contains a predominantly minority Latino population with a mostly lower socioeconomic status.

We had three hypotheses for this study:

- Advertisements displayed on bus-stop-shelter billboards in the two different neighborhoods in San Francisco would have a predominance of tobacco advertising, similar to the other types of outdoor advertising previously studied;
- Tobacco advertising would be more prevalent in the minority Latino neighborhood; and
- The tobacco advertising would target adolescents.

Methods

Census data from 1990 were used to compare the demographics of the two districts: total populations, percentage of male and female residents, percentage of persons 5 to 17 years of age, race, ethnicity, and median income levels.

A prospective study was carried out between April 1992 and March 1993. A full year was used to take into account possible seasonal and holiday changes in advertisements. Every single advertisement—two per shelter, one on each side—in every illuminated bus-stop shelter in the two different San Francisco neighborhoods was photographed and recorded each month. The locations of the bus-stop-shelter billboards were determined through a list maintained by the San Francisco Municipal Railway. A total of 16,457 daily revenue public transportation miles were scheduled in the Mission District, versus 15,405 miles in Eureka Valley.

Data were collected on type (Table 1) and frequency (Table 2) of the products advertised. Initial classification of the advertised products was based on previous methods[32] and subsequently modified to include certain advertisements, such as those related to the acquired immunodeficiency syndrome, which we thought should constitute a separate category. Advertisements were classified into 12 different categories (see Table 1). In addition, the content of the tobacco advertisements was analyzed qualitatively—language, theme, image—based on previous methods and findings.[19,36-39] We individually categorized each advertisement for product type and subsequently categorized all tobacco advertisements qualitatively. Two other raters, a family nurse practitioner and a middle-school science teacher, neither of whom had any knowledge of the hypotheses of the study, also independently classified the advertisements. Inter-rater reliability of advertising content was 98%.

A total of 23 illuminated bus-stop-shelter billboards with about 46 advertisements were sampled monthly in the Eureka Valley District. A total of 50 illuminated bus-stop-shelter billboards, with about 100 advertisements, were sampled monthly in the Mission District. Over the course of the 12-month study period, data were obtained regarding about 552 advertisements in the Eureka Valley District and 1,200 in the Mission District.

TABLE 1.—*Bus-Stop-Shelter Billboard Advertising**

Category of Advertising	*Product Type*
Tobacco	Cigarettes, chewing tobacco, and snuff
Alcoholic beverages	Beer, wine, and hard liquor
Local business	Businesses located or headquartered in San Francisco, including restaurants, clothing and department stores, hospitals, and retail manufacturers
Local event	Discrete events including museum exhibits, concerts, park and recreation activities, and fundraisers
Transportation	Public transportation advertisements
Community service	Youth hot lines, reducing hunger, immunizing children, and antidrug messages
National or international business	Businesses not based in San Francisco, but advertising their products here
Movies	All movie advertisements
Blank	Shelters temporarily without billboards; out of service or no longer exist; shelters removed due to street or building construction
AIDS	Public service advertisements concerned with the acquired immunodeficiency syndrome epidemic, human immunodeficiency virus issues, and safe sex
Antismoking	California Department of Health antitobacco ads
National government	Political, Immigration and Naturalization Service, and the Internal Revenue Service

*Modified from the Centers for Disease Control and Prevention.[13]

Data were also obtained about adolescents' possible exposure to the bus-stop-shelter billboards, including the locations and enrollments of neighborhood schools, teen clubs and other adolescent-oriented recreation spots, and public transportation lines leading to these areas.

Results

Based on 1990 census data, the population for Eureka Valley was 49,240, compared with 52,911 for the Mission. In the Eureka Valley, 54% of the population was male versus 44% in the Mission. In the Eureka Valley, 7% were 5 to 17 years old versus 14% in the Mission. Eureka Valley was 75% white, 19% Hispanic, 4% African American, and 2% Asian-Pacific Islander. The Mission was 49% Hispanic, 40% white, 4% African American, 4% American Indian-Eskimo-Aleut, and 3% Asian-Pacific Islander. The median income level was $36,943 for Eureka Valley versus $25,516 for the Mission.

Of the 1,200 bus-stop-shelter billboard advertisements in the Mission District, 9% promoted tobacco use, as did 11% of the 552 advertisements in the Eureka Valley District. Tobacco advertisements were exclusively for cigarettes and were the single most commonly advertised product. Phillip Morris was the company responsible for all tobacco advertisements, with the following brand names (in decreasing order of frequency): Marlboro, Virginia Slims, Merit, Benson & Hedges, and Bucks. Fewer than 2% of all advertisements in the Mission contained California Department of Public Health antismoking messages, compared with fewer than 1% in Eureka Valley. The number of bus-stop-shelter billboard advertisements was approximately 1 per 1,000 in Eureka Valley versus 2 per 1,000 population in the Mission. Large differences occurred in advertisements for the following categories: local businesses (32% for Eureka Valley versus 13% for the Mission), community services (31% for the Mission versus 9% for Eureka Valley), national businesses (31% for the Mission versus 9% for Eureka Valley), and blank or out-of-service, no longer exists (16% for Eureka Valley and 6% for the Mission). Differences between the two districts for other categories were 2% or less.

In 1993 the neighborhood school enrollment in the Mission was 1.5 times that of Eureka Valley. There were eight times as many clubs and service organizations for adolescents in the Mission as in Eureka Valley.

Qualitative analyses revealed no differences between the tobacco advertisements on the bus-stop-shelter billboards versus the other two forms of outdoor advertising and primarily targeted adolescents. Marlboro was represented by the "Marlboro Man," shown engaging in activities involving adventure, daring, and recreation. Virginia Slims was represented by thin, glamorous women—white, African American, and Latina—all professionally and fashionably dressed or in elegant party clothes, enjoying a social situation. Merit was represented with modern design graphics containing clean, sharp lines and bright colors. Benson & Hedges was also represented with modern design graphics containing ele-

TABLE 2.—*Total Percentage for All 12 Categories of Advertisements From April 1992 Through March 1993* in 2 San Francisco Neighborhoods*

	San Francisco District	
Category	*Mission, %*	*Eureka Valley, %*
Tobacco	9	11
Alcoholic beverage	7	4
Local business	13	32
Local event	1	3
Transportation	1	0
Community service	31	9
National or international business	21	12
Movies	3	5
Blank	6	16
AIDS	8	7
Antismoking	2	<1
National government	1	1

AIDS = acquired immunodeficiency syndrome

*Note that the percentages are rounded to the nearest whole number, so they may not add up to 100. There are 1,200 total advertisements for the Mission District and 552 for Eureka Valley.

gant backgrounds with deep, rich colors. Bucks was represented by a mature, antlered deer in its natural, wild environment.

Discussion

Bus-stop-shelter advertising is a particularly focal form targeting neighborhoods. Our study showed that these two neighborhood commercial districts had similar amounts of tobacco advertising, comprising more than 10% of all advertisements. This was surprising as we had expected that the predominantly minority Hispanic, lower-income Mission District would have a higher frequency of tobacco advertisements than the predominantly white, higher-income Eureka Valley. The youth and adolescent population living in the neighborhoods with possible exposure to these advertisements was twice as large in the Mission as in Eureka Valley—14% versus 7%. Tobacco advertising was the single most common advertisement for any one specific business type, product, or service. In addition, tobacco advertisements were specifically located at some of the busiest intersections in both neighborhood commercial districts, thus ensuring maximal 24-hour exposure. All major public transportation routes in both neighborhoods passed by shelters with tobacco advertisements. All transportation routes to and from local schools and adolescent-oriented clubs and organizations passed by shelters with tobacco advertisements. There was potential additional exposure in the Mission due to the higher school enrollment and predominance of adolescent-oriented clubs and service organizations.

Advertising tobacco in the context of other businesses and services helps legitimize tobacco use.[3] In this specific context of neighborhood advertising of a variety of products and services both locally and nationally based, the use of tobacco may seem particularly legitimate. The heavier advertising of national and international businesses in the Mission District for products that are better known and widely used may especially emphasize the "normality" of tobacco use. Those who live, work, play, attend school, or rely on public transportation in these neighborhoods are particularly exposed to this form of media "education." The themes promoted by the tobacco advertisements, such as "looking good," success, adventure, and healthy fun, are known to appeal to adolescents; persuasive communication is to promise a reward and to connect the reward with the use of the product.[35] The company that leases the billboards states in its promotion for the Mission District (Gannett Transit Shelter Company of San Francisco, Promotional Material, 1990, 1993):

> We have transit shelters at almost every bus stop within the Latino community, where there is an exceptionally heavy amount of transit use as well as large amounts of pedestrian traffic. The large vertical format and back-lit illumination of Shelter Posters afford the advertiser spectacular impact and round-the-clock viewing. Shelter Posters reach the Hispanic community where they live, work, and play.

Although we studied only two neighborhood commercial districts, it is likely that this type of advertising is widely used by tobacco companies. Similar research in other neighborhoods and in other cities would be useful to document the prevalence of tobacco company use of this medium. Clearly in these two neighborhoods in San Francisco, bus-stop-shelter billboard advertising is one of the newer and more insidious methods used by tobacco companies to promote tobacco use. This form of advertising specifically targets adolescents and minorities in their own neighborhoods. As the Surgeon General has declared, "the most effective preventive programs are community-wide ones that combine education and public policy approaches."[13,21] On an educational level, to prevent tobacco use during childhood and adolescence, it is important to use family, clinical, and programmatic approaches to address and counter media advertising and images.[9,40-44] On a local public policy level, we will propose to the San Francisco Board of Supervisors that tobacco advertising be banned from bus-stop-shelter billboards based on the results of this study, and we urge physicians and educators to act similarly in their own communities.

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Conferences and Reviews

Enigmas in Sarcoidosis

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Sarcoidosis is a multisystem granulomatous disorder of unknown cause that presents most frequently in young adults with bilateral hilar adenopathy, pulmonary infiltrates, and skin or eye lesions. The multisystem clinical manifestations of this disease are a diagnostic challenge to all physicians. Although the clinical and pathologic characteristics of sarcoidosis are well described, the decision to treat and the optimal therapy are less well defined. This review focuses on the natural history, clinical manifestations, controversies in therapy, including steroid-sparing agents, and current concepts of how the disease's activity can be monitored.

(Chesnutt AN: Enigmas in sarcoidosis. West J Med 1995; 162:519-526)

Sarcoidosis is a multisystem granulomatous disorder of unknown cause that occurs most frequently in young adults and presents as bilateral hilar adenopathy, pulmonary infiltrates, and skin or eye lesions. In Greek, *sarco* means "flesh," *eidos* means "like," and *osis* means "condition"; thus, flesh-like condition. The cause remains an enigma. The multisystem involvement of this disease challenges the clinical acumen of all physicians, regardless of their subspecialty.* Sarcoidosis can affect virtually any organ. Many patients are asymptomatic, and the disorder is discovered only by incidental chest radiograph. In most patients, their illness resolves spontaneously.

Epidemiology

The epidemiologic features of sarcoidosis vary widely among countries and ethnic groups. Scandinavian countries, the United States, England, and Japan have the highest prevalence. The incidence in Sweden is estimated at 64 per 100,000; in the United States it is 11 per 100,000.[1] In the United States the prevalence among African Americans is ten times that among whites. African-American women are affected twice as frequently as African-American men. Interestingly, sarcoidosis is rare in African blacks. It is also rare in the Chinese and Greeks. The incidence peaks between 20 and 30 years of age; a second peak in women between 45 and 65 years accounts for a slight female predominance.

Pathogenesis

The cause of sarcoidosis remains one of the mysteries of modern medicine. Many experts think it is a syndrome that has many precipitating agents, but others believe it has a single antigenic agent yet to be determined. Investigators have studied the following possible causes: infectious agents, including mycobacteria, fungi, viruses, and retroviruses; allergens, including pine pollen, chemicals, and drugs; autoimmunity; and genetic factors.

Mycobacterial disease has recently reemerged as a possible etiologic agent. Early studies reported the high incidence of serum antibodies against mycobacterial antigens and mycobacteriophages in patients with sarcoidosis.[2,3] Recent advances in the techniques of molecular biology have resurrected this old theory. One study used the polymerase chain reaction to detect mycobacterial DNA in clinical specimens from patients with sarcoidosis.[4] *Mycobacterium tuberculosis* DNA was found in half of the patients with sarcoidosis. These results have been contradicted by three other groups, however.[5-7] Nonetheless, many investigators believe in a causal relationship between mycobacterial infection and sarcoidosis.

The non-necrotizing granuloma that characterizes sarcoidosis consists of a central follicle of macrophages and multinucleated giant cells surrounded by a perimeter of lymphocytes, monocytes, and fibroblasts (Figure 1). These granulomata are typically located in three regions of the lungs: the subpleural and peribronchial spaces and the interlobular septa. The main immunologic abnormalities are anergy in a considerable proportion of patients (50% to 60%), a decreased number of peripheral blood CD4 lymphocytes, and an increased number of CD4 lymphocytes at sites of involvement.[8] One current theory proposes that an unknown antigen, probably delivered to the lungs through inspired air, activates T cells and macrophages. These cells then release chemotactic factors and cytokines, which promote an inflammatory response in the lungs resulting in a lymphocytic alveolitis. The alveolitis then sets the stage for granuloma formation. Activated T cells of the granuloma migrate to the rest of the body through the bloodstream or lymphatic

*See also the editorial by O. P. Sharma, MD, "Whither Sarcoidosis?" on pages 553-554 of this issue.

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
BAL = bronchoalveolar lavage
CT = computed tomography
HIV = human immunodeficiency virus

vessels. The granuloma can resolve with the restoration of normal lung architecture, can persist for months to years, or can progress to scarring and fibrosis.[9]

Why some patients have complete and spontaneous resolution of their disease while in others pulmonary fibrosis and severe systemic disease develop is an enigma. The sequence of events leading to pulmonary fibrosis in patients with sarcoidosis is an area of active investigation. Research has focused on the mechanisms of lymphocyte-endothelial cell recognition and lymphocyte binding to specific adhesion molecules leading to CD4 compartmentalization at sites of involvement. The exaggerated immunologic response in host tissue alters the normal architecture and triggers intrinsic host repair processes. These processes include fibroblast migration and collagen and matrix synthesis.

Radiographic Staging

Sarcoidosis is staged on the basis of radiographic criteria. Stage 0 is a normal chest radiograph. Stage I is bilateral hilar adenopathy (Figure 2). Stage II is bilateral hilar adenopathy with diffuse parenchymal infiltrates (Figure 3). Stage III is diffuse infiltrates without adenopathy (Figure 4). Stage IV is lung fibrosis. About 8% of patients present with stage 0, 51% with stage I, 29% with stage II, and 12% with stage III.[10] The combination of bilateral hilar adenopathy with right paratracheal adenopathy is a fairly reliable sign of sarcoidosis. The parenchymal infiltration patterns in stages II and III of sarcoidosis can be grouped into reticulonodular, acinar, and large nodules. There are some limitations to this staging system. The chest radiographic findings do not necessarily correlate with clinical presentation, pulmonary function, or disease, and they are limited in the assessment of parenchymal disease. For example, in 70% of patients with bilateral hilar adenopathy on chest x-ray film (stage I disease), parenchymal granulomas can be demonstrated by transbronchial biopsy.[11]

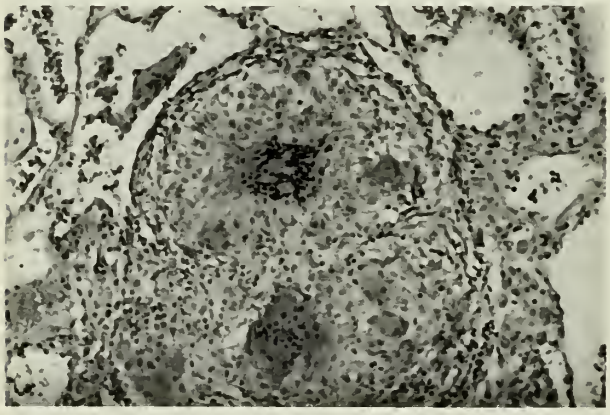

Figure 1—The lung biopsy specimen shows non-necrotizing granulomata (hematoxylin and eosin stain; original magnification × 25).

Computed tomography (CT) has advanced the diagnosis of parenchymal disease. When parenchymal involvement cannot be seen on chest radiographs, it can often be demonstrated on CT scan of the chest and, specifically, high-resolution CT scanning. In one prospective study of high-resolution CT scanning, 6 patients with stage I findings on radiographs had parenchymal nodules on high-resolution CT.[12] The classic findings were as follows: peribronchovascular nodules, irregular septal thickening, subpleural nodules, and ground-glass opacity (Figure 5).

Natural History

The natural history of this disease, particularly when it presents as stage I or II, is one of spontaneous regression. The available information is derived mostly from studies that evaluated radiographic resolution of disease in both treated and untreated patients. In 1959 spontaneous remission rates were reported in 61% of untreated patients observed over two years with stage I and 41% with stage II and III disease combined.[13] Taking into account all stages, about two thirds of patients will have spontaneous resolution of their disease; about a third of patients will have a smoldering course. Functional impairment due to sarcoidosis will develop in only about 15% to 20% of all patients. The current staging system does correlate with the prognosis; stage I patients have the highest remission rate and stage III the lowest. Table 1 shows the radiographic resolution of three stages in a cohort of patients observed for 15 years in Sweden.[14]

Clinical Manifestations

Pulmonary

The most common organ system involved is the respiratory tract, and the most common symptoms are dyspnea, cough, and chest pain; hemoptysis is rare. The chest radiographic changes have already been discussed. Other less common radiographic manifestations include pleural effusion, pneumothorax, and cavitation. Unilateral hilar adenopathy is seen in 3% to 5% of patients.[15]

Pulmonary function tests usually show a restrictive pattern with reductions in lung volumes and an impaired diffusing capacity.[16] Some patients have normal static pulmonary function but impaired function on exercise.[17] Similar to the radiographic abnormalities, the physiologic disturbance usually resolves spontaneously, but irreversible pulmonary changes develop in about a third of patients and severe disability in 10% to 15%.

Dermatologic

About a quarter of patients will have one of five major dermatologic manifestations: erythema nodosum,

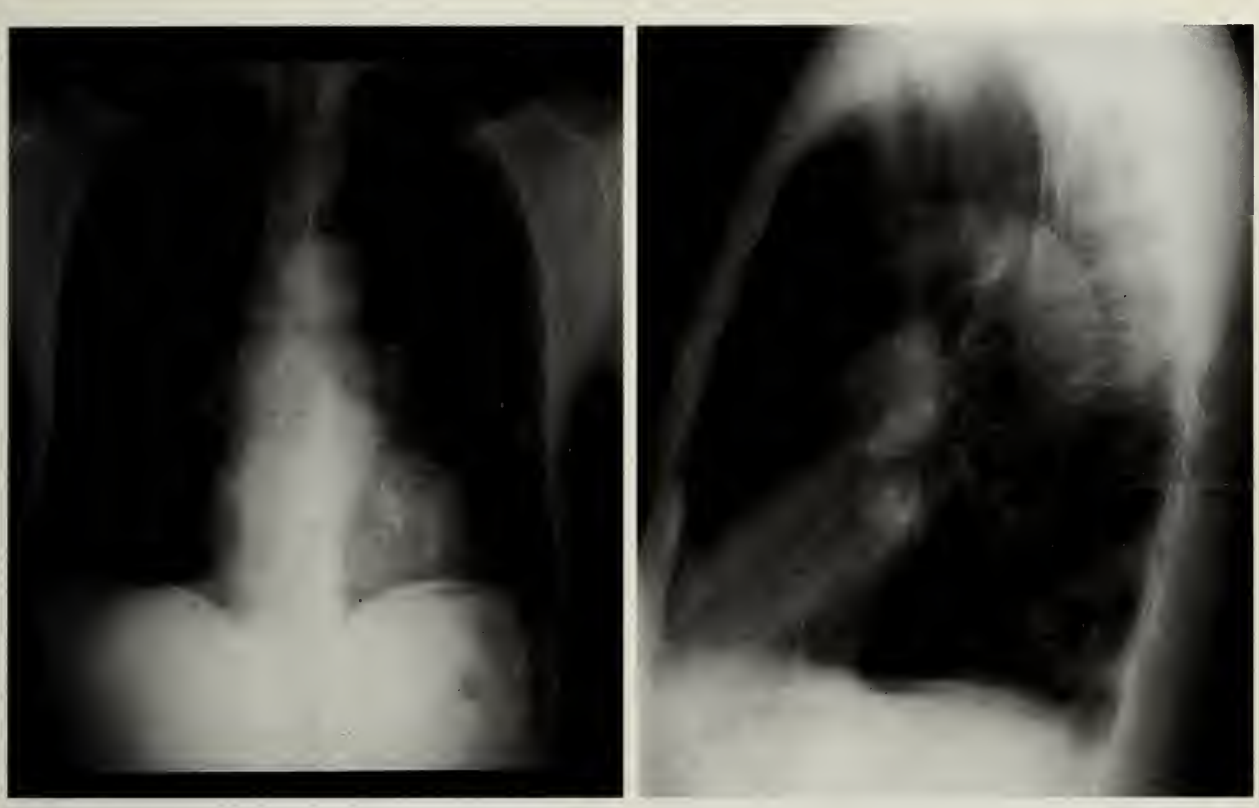

Figure 2.—Chest radiographs are shown from patients with stage 1 sarcoidosis: **Left,** A posteroanterior view of the chest is shown. **Right,** A lateral view shows impressive hilar adenopathy.

nodules, maculopapular eruptions, plaques, and lupus pernio.[18] Erythema nodosum is a panniculitis characterized by painful, raised erythematous nodules, usually in the lower extremities. Lofgren's syndrome is acute sarcoidosis characterized by fevers, myalgias, erythema nodosum, and bilateral hilar adenopathy. Maculopapular eruptions and plaques are the most common manifestation and usually appear on the extremities. Lupus pernio is the most specific cutaneous lesion; it is a chronic, violaceous lesion of the nose, cheeks, and ears and is associated with chronic sarcoidosis.

Ocular

About 25% of patients will have one of the following: anterior uveitis, posterior uveitis, conjunctival lesions, and scleral plaques.[19] Anterior uveitis is in the differential diagnosis for a painful red eye. Slit-lamp examination reveals characteristic cells in the anterior chamber. Because uveitis can lead to permanent blindness and can often have a paucity of clinical symptoms, it is imperative that all patients undergo formal eye examinations even if asymptomatic.

Cardiac

At autopsy about 25% of patients have granulomatous inflammation of the myocardium, but only about 5% of patients will have clinically evident disease.[20] This typically results from granulomas infiltrating the myocardium, causing disruption of the normal conduction system. Thus, the most common modes of presentation are complete heart block, cardiac arrhythmias, and sudden death.[20] In rare cases inflammation can also lead to ventricular scarring and congestive heart failure. Pulmonary hypertension is usually due to severe restrictive lung disease.

Gastrointestinal

As many as 75% of all patients will have asymptomatic liver granulomas, but only 20% will have abnormal results on liver function tests.[21] The most common abnormality is an elevated alkaline phosphatase level. Most patients do not have abdominal symptoms or signs. The converse situation is when granulomas are found on a liver biopsy. The differential diagnosis of liver granulomas is often a perplexing issue. In one large series of 565 patients with hepatic granuloma, the causes were sarcoidosis (38%), underlying liver disease such as primary biliary cirrhosis (31%), tuberculosis (12%), and schistosomiasis (3%).[21]

Neurologic

Neural involvement in sarcoidosis is rare (only 5%), but is important when it occurs. Cranial nerve palsy is the most common manifestation, often a seventh nerve palsy.[22] Other manifestations include aseptic meningitis, hydrocephalus, peripheral neuropathy, and hypothalamic and pituitary gland dysfunction. Cerebrospinal fluid abnormalities include elevated protein levels and pleo-

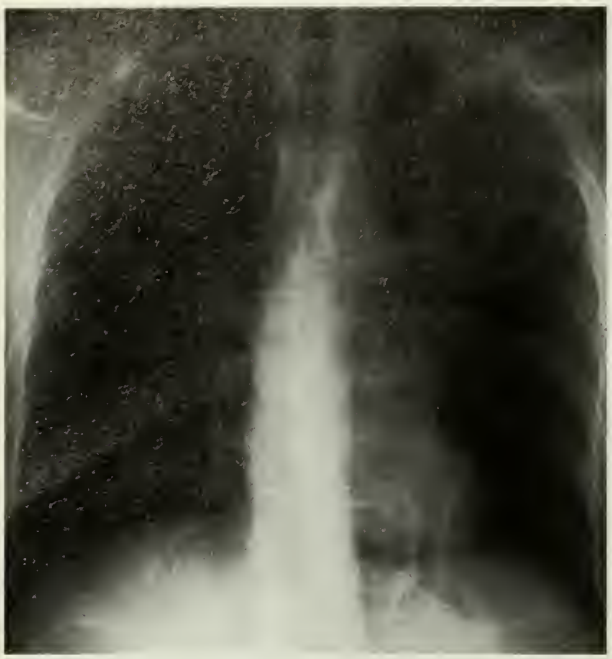

Figure 3.—The posteroanterior view of the chest shows stage II sarcoidosis.

Figure 4.—The posteroanterior view of the chest shows stage III sarcoidosis.

cytosis. A chronic relapsing course is fairly common for neurosarcoidosis. It also has a higher mortality rate than other forms of sarcoidosis.

Endocrine

Hypercalcemia is present in 11% to 17% of patients.[23] The mechanism of hypercalcemia is fascinating. In normal vitamin D metabolism, vitamin D is converted by the liver to 1-hydroxyvitamin D and then by the kidney to 1,25-dihydroxyvitamin D_3 or calcitriol. This is the most potent metabolite of vitamin D and stimulates intestinal absorption of calcium. In sarcoidosis, the alveolar macrophages secrete 1,25-dihydroxyvitamin D_3, and they seem to secrete it independent of feedback inhibition and parathyroid hormone. Steroids block the peripheral action of calcitriol, converting it to an inactive form, and are effective in controlling the hypercalcemia of sarcoidosis.[24] Other rare manifestations include the syndrome of inappropriate secretion of antidiuretic hormone and diabetes insipidus from hypothalamic and pituitary involvement, hyperthyroidism, and hypothyroidism.[23,25]

Rheumatologic

About 10% to 20% of patients will have arthralgias or arthritis. Involvement of skeletal muscle can present as acute polymyositis, chronic myopathy, and muscle nodules. Radiographs of the hands show characteristic lytic lesions in phalangeal heads that become corticated, forming bone cysts.

Renal

At autopsy granulomas are found in the kidneys in about 20% of patients, but they are rarely clinically evident.[26] Nephrocalcinosis due to hypercalcemia and hypercalciuria is the most common renal manifestation of sarcoidosis, followed by granulomatous nephritis, glomerular disease, and renal arteritis.[26]

Hematologic

Lymphadenopathy occurs in about 75% of all patients, and leukopenia, lymphocytopenia, and an elevated erythrocyte sedimentation rate are common. Anemia is rare. Bone marrow granulomas are occasionally noted at autopsy. In one extensive review of granulomatous bone marrow disease, however, only 4 of 58 patients (7%) had sarcoidosis.[27]

Miscellaneous

Sarcoidosis of the upper respiratory tract is seen in 6% of cases. Granulomas can be found in the nasal mucosa, larynx, and pharynx. Symptomatic nasal granulomas are an indication for steroid therapy.[28] Parotid gland enlargement is noted clinically in only about 6% of cases, but increased gallium uptake is noted in about 75% of cases. Many cases have been reported in the literature of sarcoidosis affecting virtually any organ, including the male reproductive organs, the uterus, and mammary glands (Table 2).[1]

Diagnosis and Evaluation

The diagnosis of sarcoidosis is based on the clinical presentation and course over time, the exclusion of other granulomatous diseases, and in most cases, tissue confirmation of non-necrotizing granulomas. Sarcoidosis usually presents with either pulmonary symptoms such as cough and dyspnea or as an incidental abnormal finding on chest radiograph in an asymptomatic person.[29] About 20% to 40% of patients with sarcoidosis will be asymp-

Figure 5.—High-resolution computed tomographic scanning shows peribronchovascular nodules and irregular septal thickening.

tomatic, and it will be discovered only through an incidental chest radiograph (Table 3). Not surprisingly, studies of patients seen at a referral center have fewer asymptomatic patients (about 20%[30]) than do studies from nonreferral institutions or population surveys (35% to 40%).[31]

The differential diagnosis of non-necrotizing granuloma is extensive, but can be grouped into five broad categories. The most important diseases to exclude are infection and neoplasm. There is no diagnostic test for sarcoidosis, so its diagnosis depends on reasonably excluding other disorders by a careful history and physical examination, including an occupational history, routine laboratory tests including a serum calcium level, chest radiograph, and a tuberculin skin test with controls. About half of patients with sarcoidosis will be anergic. Most patients should also have a slit-lamp evaluation of their eyes and pulmonary function tests as part of a baseline evaluation. Even asymptomatic patients may have mild restriction or a diminished diffusing capacity, and this information may be important in guiding management.

Sarcoid granulomas are typically widespread, so possible sites for biopsy include lungs, liver, skin, lymph nodes, salivary glands, and conjunctivae. Obviously the choice of site should be guided by the physical examination findings, and biopsy of a node or skin lesion should be simple. Biopsy of these areas is more likely to yield a falsely positive result, but in appropriate clinical situations abnormal findings on a biopsy permit a clinical diagnosis. In the absence of clinical evidence of involvement of easily biopsied tissues, the important point to remember is that transbronchial biopsy is diagnostic in 60% to 70% of patients without chest radiographic evidence of parenchymal disease (stage I) and in 85% to 90% of patients with abnormal parenchyma on chest radiographs.[11] In most patients transbronchial biopsy is the most direct way to obtain tissue.

The question of whether asymptomatic patients with bilateral hilar adenopathy need a tissue diagnosis is somewhat controversial. In the early 1970s, 100 cases of bilateral hilar adenopathy were retrospectively reviewed.[29] The 74 patients who had sarcoidosis were either asymptomatic, had normal findings on physical examinations, or had erythema nodosum or uveitis. Almost all the patients with bilateral hilar adenopathy and cancer had symptoms or abnormal physical findings. The study concluded that patients with bilateral hilar adenopathy who were asymptomatic or had erythema nodosum or uveitis did not require tissue confirmation and could be observed closely. Several arguments oppose this approach. Of note, this study was conducted at a private Seattle clinic; in inner-city hospitals with a higher incidence of infectious processes and less certain follow-up, tissue biopsy may be warranted. This study was also done before the era of human immunodeficiency virus (HIV) infection. Many opportunistic infections and malignant neoplasms in patients with HIV elicit thoracic adenopathy. In addition, many patients simply want to know that they do not have cancer or tuberculosis. Finally, many authors feel that the third element of the diagnosis of sarcoidosis, "reasonable exclusion of other granulomatous disorders," requires negative fungal and acid-fast bacilli stains of tissue. In summary, although it may be reasonable to defer a tissue diagnosis in a reliable, asymptomatic patient without HIV risk factors, in the vast majority of patients a tissue diagnosis should be pursued. Clearly, any patient being considered for corticosteroid therapy should have a tissue biopsy.

Elevated levels of serum angiotensin-converting enzyme (ACE) can support the diagnosis of sarcoidosis. Angiotensin-converting enzyme is produced by the epithelioid cells of the granuloma and reflects total body granuloma load. These levels are elevated in about 70% of patients with sarcoid. The enzyme is nonspecific, and elevated levels can also be seen in patients with cirrhosis, diabetes mellitus, silicosis, coccidioidomycosis, and hypersensitivity pneumonitis. Serum ACE measurement has a false-positive rate of 10% and a false-negative rate of 40%. Therefore, it cannot be used as a definitive diagnostic test, but it can add information. Studies using ACE levels to follow patients' response to corticosteroid therapy are conflicting, but some patients show decreased ACE levels with therapy.

Therapy

Who should be treated? The answer to this question is the most controversial in the literature on sarcoidosis. Corticosteroid therapy has been used since 1952 and benefits some patients initially, such as those with involvement of vital organs (eyes, heart), severe systemic symptoms, or overwhelming involvement of the lungs. Administering corticosteroids decreases the number of CD4 cells in the lungs. It may also cause alveolar macrophage release of tumor necrosis factor. The goals of therapy are to lessen symptoms and to prevent fibrosis. Several randomized, controlled trials done in the

TABLE 1.—*Radiographic Resolution of Sarcoidosis**

Stage	*Degree of Resolution*
I	50% after 15 months
II	50% after 36 months
III	33% after 5 years

*Adapted from Hillerdal et al.[14]

1950s, 1960s, and 1970s are fraught with the problems of small numbers of patients and varying doses and duration of steroid therapy.[32,33] They do consistently show that during the treatment period, patients respond to steroids with abatement in clinical symptoms and chest radiograph findings and improved pulmonary function. No controlled trial has shown that steroids alter the long-term outcome, however. Nonetheless, many case series in the natural history literature do show patients doing well on steroid therapy.

The indications for treatment are symptomatic pulmonary disease, deteriorating pulmonary disease, hypercalcemia, and extrapulmonary involvement (cardiac, neurologic, ocular, or upper airways disease).[34] The treatment of asymptomatic stage II and III lung disease is controversial and is generally guided by lung function impairment as determined by serial pulmonary function testing. In a recent prospective study of 98 patients, corticosteroid treatment was limited to those with objective evidence of a deterioration in lung function over three months, defined as a 10% decrease in total lung capacity or diffusing capacity or a 15% decrease in forced vital capacity. Of the 55 patients who were observed without therapy, only 8 deteriorated; 47 remained stable or improved over an average duration of follow-up of 2 ± 0.1 years.[35] This study and previous studies have noted that many patients with major abnormalities of chest radiographs and pulmonary function testing have chronic stable disease that does not require therapy.

If treatment is to be used, there are many different protocols. A reasonable approach might be to start with a daily corticosteroid dosage of 40 mg, continue at that dosage for two weeks, and taper over the next six to eight weeks at 5- to 10-mg decrements to a maintenance dose of 10 to 15 mg. The maintenance dose should be continued for at least 6 months and the dose tapered over 12 months.[36] About 60% of patients will relapse with recurrence of symptoms and a decline in pulmonary function as steroid doses are being tapered, but usually will respond with a small increment in doses of 5 to 10 mg. Cases in which high-dose corticosteroid therapy (60 to 80 mg a day) is warranted are cardiac, neurologic, ocular, and upper airways disease.

Inhaled corticosteroids have been used in the treatment of pulmonary sarcoidosis. Many of the studies of this treatment were conducted in Europe and used inhaled budesonide, which is not available in the United States. In general, the studies showed improvements in bronchoalveolar lavage measurements of alveolitis (see Disease Activity), but not in chest radiographs or pulmonary function.[37] Further well-controlled studies are needed to address this issue. Nonetheless, it is reasonable to use inhaled corticosteroids in patients with cough, bronchial hyperreactivity, or mild pulmonary symptoms. Patients on a low maintenance dose of 5 to 10 mg for pulmonary disease may do just as well on a maintenance regimen of inhaled corticosteroids.

Steroid-Sparing Agents

Given the long-term adverse effects of corticosteroid use, there has been much investigation of alternative agents. Although this subject has been recently extensively reviewed, a brief description of the agents is warranted.[38] The general indications for steroid-sparing agents are intolerable corticosteroid toxicity, the progression of disease on steroid therapy, and in some cases, the need for long-term steroid therapy. The agents commonly considered are methotrexate, chloroquine, azathioprine, cyclophosphamide, and cyclosporine.

A recent review from the University of Cincinnati College of Medicine noted that more than 50 patients have been treated for at least two years with methotrexate with limited toxic reactions.[38] The main toxic effects are hepatic and hematologic. The antimalarial drug chloroquine has been effective in treating cutaneous sarcoidosis, especially lupus pernio, but has little effect on systemic disease. Its major toxic effect is ocular. Azathioprine is a purine analogue often used in transplant recipients. It can cause nausea, bone marrow sup-

TABLE 2.—*Clinical Manifestations of Sarcoidosis*

System	*Manifestations*
Pulmonary	Dyspnea, cough, chest pain, chest radiographic abnormalities
Dermatologic	Plaques, maculopapular eruptions, nodules, erythema nodosum, lupus pernio
Ocular	Uveitis, scleral plaques, conjunctival lesions
Cardiac	Complete heart block, arrhythmias, sudden death, heart failure, pulmonary hypertension
Gastrointestinal	Elevated alkaline phosphatase level, liver granulomas
Neurologic	Cranial nerve palsy, aseptic meningitis, hypothalamic and pituitary dysfunction, peripheral neuropathy
Endocrine	Hypercalcemia, SIADH, diabetes insipidus
Rheumatologic	Arthralgias, arthritis, bone cysts, myopathy
Renal	Nephrocalcinosis, hypercalciuria
Hematologic	Lymphadenopathy, lymphopenia, thrombocytopenia
Upper respiratory tract	Nasal granulomas, sinusitis

SIADH = syndrome of inappropriate [secretion of] antidiuretic hormone

TABLE 3.—*Clinical Presentation of Sarcoidosis**

Signs and Symptoms	*Patients, %*
Pulmonary symptoms (dyspnea, cough, chest pain)	40-50
Asymptomatic	30-40
Constitutional symptoms (fever, malaise)	20
Extrathoracic symptoms	7-10

pression, and hepatic toxicity. Anecdotal reports have been promising, but further studies are needed. Treatment for six months is recommended. Cyclophosphamide is an alkylating agent used in the treatment of idiopathic pulmonary fibrosis. Its use in sarcoidosis has been limited. Cyclosporine is a potent immunosuppressive agent used to treat transplant recipients. Its use in sarcoidosis has been disappointing overall. It has been useful in patients who underwent liver transplantation for sarcoidosis after having recurrence in the allograft.[39]

Finally, organ transplantation is a viable alternative for patients with cardiac, hepatic, and pulmonary sarcoid. The granulomas of sarcoidosis often recur in the allografts but can be suppressed given the high doses of immunosuppressive agents used in these patients. Clinically important organ dysfunction in the allografts appears to be rare.

Disease Activity

The concept of disease activity refers to activated inflammatory cells and the maintenance of granuloma formation as opposed to inactive disease that has produced scarring and fibrosis. It differs from the extent of disease and functional impairment. For example, a 30-year-old man with cough, dyspnea, and stage II sarcoidosis by radiograph might have disease limited to the lungs based on a routine evaluation. Like most patients with sarcoidosis, this patient is young and is only mildly functionally impaired by his symptoms. He may, however, have acute active disease that will progress if untreated. Thus, a patient can have active sarcoidosis that is limited to the lungs and does not cause severe functional impairment. Monitoring his response to therapy essentially requires monitoring disease activity. The modalities include clinical symptoms, chest radiograph, CT scan, pulmonary function tests, serum ACE levels, gallium scan, and bronchoalveolar lavage.

Many patients on steroid therapy feel subjectively better; therefore, while lessening of clinical symptoms is an important monitor of response, some objective data are also often necessary. Radiographs may show resolving parenchymal disease. Pulmonary function tests are noninvasive and are helpful in objective measurement. Serum ACE measurement has been discussed, and in many patients it is helpful in monitoring response and predicting relapse. Some patients with acute sarcoidosis will not have an initial elevated level, and thus it is rarely helpful in such patients. Recent studies in the radiol literature are investigating the correlation between hi resolution CT findings, pulmonary function tests, gallium scans. There appears to be a characteristic "ground-glass" pattern on high-resolution CT scan that may correspond to acute alveolitis (see Figure 5). More studies need to be done before we can use this study routinely.

Gallium citrate Ga 67 is taken up by active sarcoid granulomas, and gallium scans are positive in about two thirds of patients. Uptake is compared with the background uptake by the liver. It is nonspecific, and uptake occurs in infections (pneumonia), neoplasm, pneumoconiosis, and idiopathic disease—systemic lupus erythematosus, pulmonary fibrosis. Although it may help in certain difficult clinical situations, its frequent routine use is not recommended because of radiation exposure.

Bronchoalveolar lavage (BAL) has allowed investigators to elucidate the cellular immune response in the alveoli. Many researchers have quantified the intensity of the alveolitis in the percentage of T cells, specifically CD4 cells, and used this measurement as a marker of disease activity. Unfortunately, the studies show conflicting results, so at present it is not used routinely.[40-42] Thus, a single analysis of the types of cells in the initial BAL is rarely helpful in predicting the course of the disease. Some investigators think that serial lavages and analysis of lavage cells may help guide therapy, but there are no conclusive data to demonstrate that BAL can accurately predict steroid responsiveness in sarcoidosis.[43(p408)]

Finally, in the current atmosphere of cost containment, it is important to realize that patients will need only a few of the aforementioned tests. A thorough review of symptoms, pulmonary function tests, and a chest radiograph will give the physician a good index of disease activity, supplemented when needed by tests such as ACE measurement, high-resolution CT and gallium scanning, and BAL.

Conclusion

Sarcoidosis remains one of the most challenging diseases in medicine. It can affect any organ system in the body and present with a wide variety of signs and symptoms. Whereas spontaneous resolution of disease is the rule, 5% to 8% of patients will eventually die of the disease, with respiratory failure being the principal cause of death. Although there have been many advances in the understanding of the pathogenesis and treatment of sarcoidosis, there remain many enigmas. The search for an etiologic agent or agents continues. Advances in immunology and molecular biology have allowed better insight into lymphocyte and macrophage signaling and activation processes and migration, which may help further elucidate the pathogenesis of sarcoidosis. In the area of treatment, studies are needed to standardize treatment indications and protocols and to determine whether long-term treatment is of benefit. Newer tests for sarcoidosis that can predict level of activity or prognosis are also needed.

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Surgical Management of Portal Hypertension

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Portal hypertension is frequently complicated by upper gastrointestinal tract bleeding and ascites. Hemorrhage from esophageal varices is the most common cause of death from portal hypertension. Medical treatment, including resuscitation, vasoactive drugs, and endoscopic sclerosis, is the preferred initial therapy. Patients with refractory hemorrhage frequently are referred for immediate surgical intervention (usually emergency portacaval shunt). An additional cohort of patients with a history of at least 1 episode of variceal hemorrhage is likely to benefit from elective shunt operations. Shunt operations are classified as total, partial, or selective shunts based on their hemodynamic characteristics. Angiographically created shunts have been introduced recently as an alternative to operative shunts in certain circumstances. Devascularization of the esophagus or splenectomy is done for specific indications. Medically intractable ascites is a separate indication for surgical intervention. Liver transplantation has been advocated for patients whose portal hypertension is a consequence of end-stage liver disease. In the context of an increasingly complex set of treatment options, we present an overview of surgical therapy for complications of portal hypertension.

(Collins JC, Sarfeh IJ: Surgical management of portal hypertension. West J Med 1995; 162:527-535)

The portal vein, which provides the principal venous drainage for the splanchnic circulation, arises behind the head of the pancreas where the superior mesenteric and splenic veins join. It courses to the porta hepatis with the proper hepatic artery and common bile duct. Anatomic connections between the portal and systemic circulations exist at the level of the hepatic sinusoids, the gastroesophageal junction, the hemorrhoidal plexus in the rectum, and the Retzius veins in the retroperitoneum. When portal pressure is elevated long term, a patent umbilical vein may direct portal blood into systemic veins within the abdominal wall, resulting in the physical findings of a caput medusae and, often, a venous hum (Cruveilhier-Baumgarten syndrome).

Portal pressure is expressed conveniently as corrected portal pressure (portal pressure minus central venous pressure). The relationship between pressure, flow, and resistance in a circuit is defined by Ohm's law—pressure equals flow times resistance. Normal corrected portal pressure (<10 mm of mercury) increases in proportion to the resistance to the flow of blood from the splanchnic to the systemic venous circulation. Pressure also increases when flow increases. Under conditions of extreme resistance, portal pressure can exceed 50 mm of mercury, but usually collateral channels limit portal pressures to no more than 30 mm of mercury.[1]

Increased splanchnic blood flow associated with a hyperdynamic systemic circulation is commonly seen in portal hypertension.[2] This increased flow is largely shunted through collateral vessels, bypassing the liver. Flow in the portal vein itself typically is reduced in portal hypertension, but may be increased due to neurohumoral influences, which are the subject of intense investigation.[3] Eventually flow may cease or reverse direction. Prograde flow is also called hepatopedal; reversed flow is hepatofugal.

Portal hypertension is classified as presinusoidal or postsinusoidal on the basis of the anatomic location of the resistance to portal flow.[4] Prehepatic obstruction of the portal vein results from congenital atresia, thrombosis, or extrinsic compression. Intrahepatic blockages occur in cirrhosis, inborn errors of metabolism, and schistosomiasis. Schistosomiasis and biliary cirrhosis produce a presinusoidal blockage, whereas alcoholic cirrhosis produces a resistance that is primarily intrasinusoidal or postsinusoidal. Posthepatic portal hypertension is associated with the rare Budd-Chiari syndrome (thrombosis of the hepatic veins or obstruction of the retrohepatic vena cava). The underlying cause of portal hypertension influences the options for therapy. In the United States, alcoholic cirrhosis is the most common cause of portal hypertension. Our discussion is directed principally to the management of patients with this disorder.*

The most urgent indication for the surgical treatment of portal hypertension is hemorrhage. Life-threatening hemorrhage results from the rupture of thin-walled submucosal venous channels in the distal esophagus, which dilate as a consequence of elevated portal pressure and flow. These varices develop to a variable degree in the

*See also the editorial by J. M. Henderson, MD, "Portal Hypertension—The Surgical Pendulum," on pages 554-555 of this issue.

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presence of portal hypertension. Neither the severity of varices nor the likelihood of rupture is directly related to the measured portal pressure. Rather, portal pressure must be elevated above a threshold—about 12 mm of mercury—after which wall tension and local structural factors probably interact to produce hemorrhage.[5] Each episode of hemorrhage carries a mortality of about 50%. After bleeding stops, the likelihood of recurrent bleeding without specific therapy to reduce portal pressure is about 75%.[4]

Another cause of upper gastrointestinal tract bleeding in a patient with cirrhosis, more recently characterized, is portal hypertensive gastropathy, previously thought to be a form of gastritis. Portal hypertensive gastropathy has been shown to be a distinct disorder that is abolished by the reduction of portal pressure.[6] Impaired gastric mucosal barrier function, submucosal edema, and microvasculopathy are characteristic. The endoscopic appearance varies from a diffuse "snakeskin" mosaic pattern to an angry-appearing, beefy-red mucosa with active bleeding. Lesions are most commonly present in the fundus, but may extend anywhere in the stomach. Bleeding is most often chronic or transient. Massive hemorrhage is a less frequent occurrence.

Other causes of upper gastrointestinal tract bleeding are common in alcohol-dependent patients, though not directly related to the presence of portal hypertension. These include gastritis, peptic ulcer, and Mallory-Weiss tears. A thorough evaluation including endoscopic examination of the esophagus, stomach, and duodenum will secure the diagnosis in most cases. This distinction is important because the surgical treatment is different.

Ascites is produced by the transudation of fluid from serosal surfaces of bowel and liver capsule resulting from the altered Starling forces within the hypertensive portal circulation. Impaired synthesis of serum proteins due to underlying hepatic insufficiency also contributes to the formation of ascites.[7] Ascites can become massive and disabling. It can be complicated further by primary or secondary bacterial peritonitis. Outward pressure on the abdominal wall can exacerbate an umbilical hernia and promote skin breakdown, with resultant life-threatening infection of the ascitic fluid.

Child described a useful classification for patients with cirrhosis,[8] comprising the largest cohort of North Americans with portal hypertension (Table 1). This was modified by Pugh and co-workers to include additional criteria.[9] Patients can be stratified according to the Child class to predict mortality for shunt and nonshunt operations. We prefer the original Child classification to its various modifications because it is simpler and sufficiently accurate for rational clinical decision making.

TABLE 1.—*Child's Classification of Cirrhosis**

Clinical Feature	Class A	Class B	Class C
Serum bilirubin, grams/liter†	<20	20-30	> 30
Serum albumin, grams/liter†	>35	30-35	< 30
Ascites	None	Controlled	Tense
Encephalopathy	None	Controlled	Severe
Nutritional state	Normal	Adequate	Cachectic
Operative mortality (elective shunt), %	5	10	50

*Modified from Child.[8]
†To convert to conventional units (milligrams/deciliter), multiply by a factor of 0.1.

Initial Therapy for Variceal Hemorrhage

The first priorities in treating acute upper gastrointestinal tract hemorrhage of any cause are protecting the airway and establishing adequate intravenous access. To us, "adequate" means the capability to pass at least two 16- to 18-gauge peripheral catheters and possibly a 9-French introducer sheath.

Fluid resuscitation must be aggressive. A rapid transfusion of warmed whole blood or packed erythrocytes usually is indicated. The hematocrit should be maintained at or above 0.25 to 0.30 (25% to 30%) and rechecked frequently without waiting for posttransfusion equilibration of the extracellular fluid compartment. Coagulation indices—prothrombin time and partial thromboplastin time—should be measured and corrected with the administration of fresh frozen plasma and, if necessary, cryoprecipitate. Bleeding time should be measured; platelet transfusion frequently is required. Timely communication with the blood bank is of utmost importance and may be lifesaving.

A Foley catheter and hourly measurements of urine output are mandatory. Invasive monitoring should be instituted in the event of any hemodynamic instability. Hypotension, which is nearly always due to profound hypovolemic shock, should be treated with a rapid infusion of volume rather than with the administration of dopamine or adrenergic agonists. Metabolic acidosis in this setting is usually due to anaerobic glycolysis with lactate production in hypoperfused tissues; treatment is by the immediate correction of hypovolemia. Hypothermia, hypomagnesemia, and hypocalcemia will occur unless specifically prevented.

Vasopressin or one of its derivatives, usually along with nitroglycerin, is infused intravenously. Vasopressin promotes splanchnic vasoconstriction, thereby decreasing portal flow and portal pressure. Vasopressin is a nonspecific systemic arterial vasoconstrictor that also causes coronary artery vasoconstriction. Nitroglycerin is given to vasodilate the coronary arteries and the portal vein.[10] The coinfusion of intravenous vasopressin and nitroglycerin has been shown to be associated with fewer complications and better control of bleeding than the use of vasopressin alone, although the risk of death is unaltered.[11] Propranolol, a β-adrenergic antagonist, may prevent the first episode of variceal hemorrhage, but its use is not recommended for the control of acute hemorrhage.[12]

After nasogastric lavage, esophagogastroduodenoscopy is done. The site of bleeding is found, and endo-

scopic control of hemorrhage is attempted. Standard endoscopic therapy consists of intravariceal or paravariceal administration of sclerosant agents.[13] Rubber-band ligation through the endoscope has shown promise in a multicenter, randomized trial as a safer and perhaps more effective alternative to sclerotherapy.[14] In a single randomized trial, the use of emergency portacaval shunt was compared with that of endoscopic sclerotherapy for acute variceal hemorrhage.[15] Hospital mortality was equivalent—about 50% for both groups—with a lower incidence of encephalopathy in those treated by sclerotherapy. On this basis, the investigators suggested that sclerotherapy be done first and surgical shunt performed for those patients whose bleeding cannot be controlled endoscopically.

Should bleeding varices be refractory to initial measures, endotracheal intubation and gastric balloon tamponade with the Sengstaken-Blakemore tube are the next steps.[13] At this point, emergency surgical intervention is indicated and should not be delayed by further diagnostic efforts. Active resuscitation should continue until an anesthesiologist can assume care. From a surgeon's perspective, a warm and well-perfused patient has a far better prognosis than one with hypothermia, acidosis, and hypovolemia.

Operations to Reduce Portal Pressure

The portal pressure can be reduced below the critical threshold by various operative techniques. All shunts aim to reduce variceal pressures sufficiently to arrest or prevent bleeding. Surgical shunts are classified as total, selective, or partial shunts based on their specific hemodynamic properties. An angiographically placed stent, or transjugular intrahepatic portacaval shunt (TIPS), is another option that has recently become available in some centers.

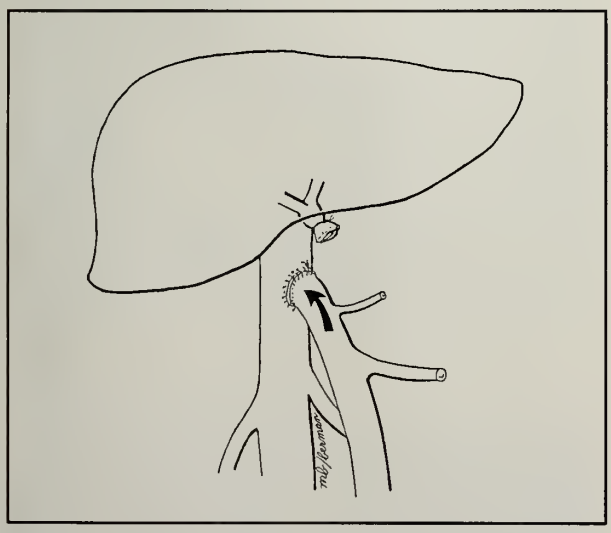

Figure 1.—*End-to-side portacaval shunt:* The portal vein is divided at the hilum of the liver, and its stump is suture ligated. The end of the portal vein is anastomosed to the side of the inferior vena cava. The direction of portal flow is indicated by the arrow. Perfusion of the liver is provided solely by the hepatic artery (not shown).

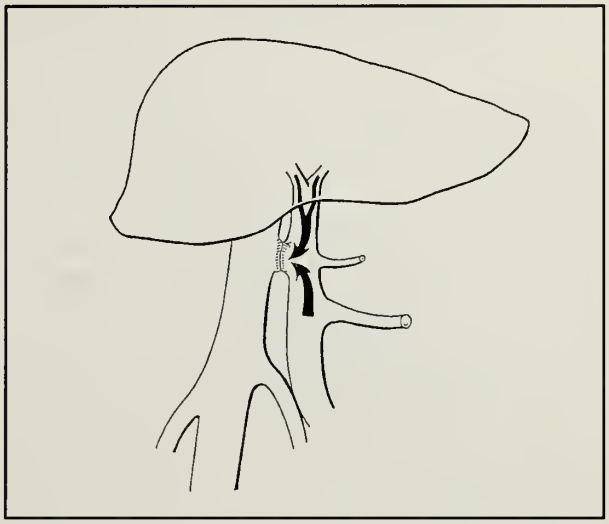

Figure 2.—*Side-to-side portacaval shunt:* The portal vein and inferior vena cava are mobilized and brought into proximity with one another. An anastomosis is created between the side of the portal vein and the side of the cava. Blood flow, indicated by the arrows, is hepatofugal.

Total Shunts

Portal blood flow can be totally diverted to the inferior vena cava by any of several techniques. Total shunts arrest hemorrhage in about 95% of cases but at the price of a 40% to 50% incidence of hepatic encephalopathy. In emergency situations, when bleeding cannot be controlled by less invasive means, total shunts may be lifesaving and encephalopathy becomes a secondary consideration.

The idea of a prophylactic shunt to protect an alcoholic patient with varices from the 50% mortality of the first variceal hemorrhage was once considered attractive. In four controlled trials in the United States that compared the use of total shunts with controls, three demonstrated poorer survival in shunted than in nonshunted patients,[16-18] and one showed no significant difference.[19] Whereas shunting decreased the risk of death from hemorrhage, deaths from liver failure overshadowed this advantage. For this reason, shunts are performed after (or sometimes during) the first episode of hemorrhage.

The end-to-side portacaval shunt (Figure 1) is performed by transecting the portal vein at its bifurcation within the porta hepatis and creating an anastomosis between the end of the portal vein and the side of the inferior vena cava. Thus, all portal flow is diverted around the liver, and the splanchnic system is totally decompressed.

Another total shunt is the side-to-side portacaval shunt (Figure 2). The difference from the end-to-side shunt is that the portal vein is not transected in the side-to-side shunt. The intact portal vein notwithstanding, pressure gradients favor hepatofugal blood flow (away from the liver) with a loss of portal perfusion. This has similar results to the end-to-side shunt—immediate cessation of

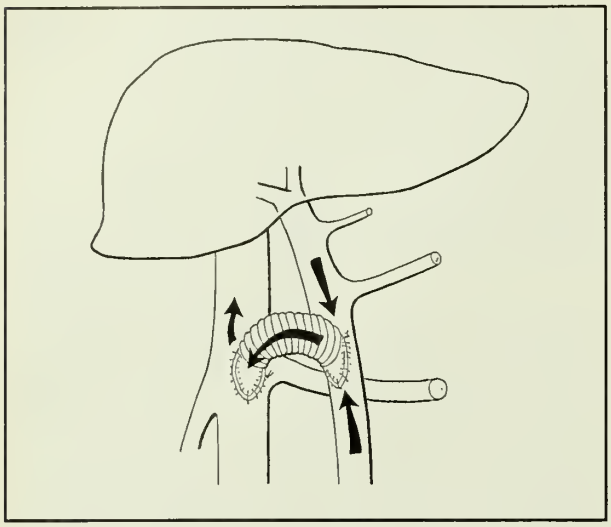

Figure 3.—*Interposition mesocaval shunt (mesocaval H graft):* The superior mesenteric vein and inferior vena cava are connected to one another by a large-diameter prosthetic conduit. The arrows indicate the direction of blood flow, which is hepatofugal.

bleeding and a high incidence of encephalopathy. A variation of this shunt is the large-diameter portacaval H graft (not shown) in which a prosthetic graft about 16 mm in diameter is used to shunt blood from the portal vein to the cava.

A third type of total shunt is the mesocaval shunt. The inferior vena cava is divided and anastomosed end-to-side to the superior mesenteric vein. Alternatively, a prosthetic graft is positioned between the superior mesenteric vein and the inferior vena cava (Figure 3). The technique is similar to the portacaval H graft. An advantage is that the shunt is far enough from the porta hepatis that the required dissection adds little difficulty to subsequent liver transplantation. A disadvantage of the mesocaval H graft is that the graft is relatively long, so there is a greater risk of graft occlusion by kinking or thrombosis. Results are similar to other total shunts.[20]

Selective Shunts

The distal splenorenal shunt (Figure 4) was developed to avoid the high rate of encephalopathy associated with the use of total shunts.[21] Anastomosing the distal splenic vein to the left renal vein selectively decompresses the gastric and splenic veins while maintaining relatively high pressures in the mesenteric and portal veins. Dividing the left gastric (coronary) vein and disconnecting the gastrosplenic and portomesenteric compartments by collateral ligation remain an important part of the procedure.[22,23]

Hepatopedal blood flow is preserved initially, with a low incidence of encephalopathy. In patients with alcoholism, collateral channels tend to dilate over time, eventually converting the selective shunt to a total one.[24] This shunt is rarely used in emergencies because portal decompression is selective, requiring time for bleeding to stop, and the procedure itself is time-consuming.

A meta-analysis of four randomized trials that compared the use of the distal splenorenal shunt with that of sclerotherapy found that the Warren shunt reduced the risk of rebleeding, did not worsen encephalopathy, and improved survival in nonalcoholic patients.[25] Patients with alcoholism did not have improved survival.

As an elective procedure in patients with portal hypertension from causes other than alcoholic cirrhosis, the Warren shunt is an effective and durable operation with extensive application worldwide. In large series, control of hemorrhage is nearly equivalent to that for total shunts (about 85%), and the incidence of encephalopathy is rare (<10%).[26] The Warren distal splenorenal shunt is particularly well suited for managing patients with extrahepatic portal vein thrombosis, of whom about 80% will have a patent splenic vein and thus be candidates for this procedure.[27]

Partial Shunts

Partial shunts were first proposed by Bismuth and associates.[28] Variceal bleeding occurs above a corrected portal pressure threshold of 12 mm of mercury.[5] Partial decompression of the portal vein to a pressure less than the critical threshold should stop variceal hemorrhage while preserving hepatopedal blood flow and preventing encephalopathy. Our investigations, based on Bismuth's concept, led to the clinical application of the small-diameter portacaval H graft.[29,30] A laboratory model predicted preserved hepatopedal flow in 50% of cases using a 10-mm conduit and in 80% using an 8-mm graft.[31] These predictions have been confirmed clinically in our center and

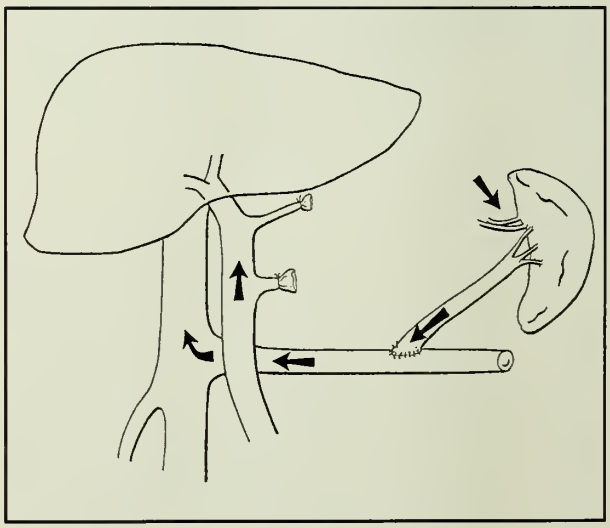

Figure 4.—*Distal splenorenal (Warren) shunt:* The splenic vein is divided near its junction with the superior mesenteric vein and dissected free of the pancreas (not shown). The end of the splenic vein is anastomosed to the distal left renal vein. Selective decompression of the gastric and splenic compartments of the splanchnic circulation is achieved. The portal and mesenteric compartments remain hypertensive. The arrows indicate the direction of blood flow. Portal flow to the liver is maintained, and gastroesophageal varices are decompressed through the spleen into the cava by the left renal vein.

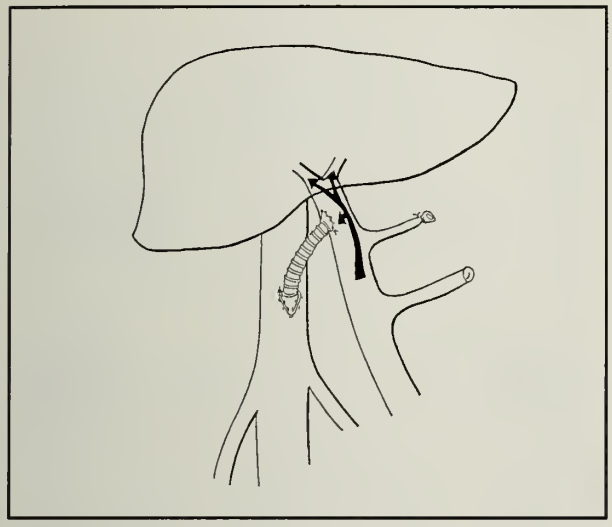

Figure 5.—*Small-diameter portacaval H graft:* The portal vein and inferior vena cava are connected by a small-diameter prosthetic graft. The portal vein is partially decompressed, and portal perfusion of the liver is preserved. The arrows indicate the typical pattern of blood flow, which is hepatopedal in 80% to 90% of patients.

others.[32-35] The small-diameter portacaval H graft consists of a short piece of ringed, expanded polytetrafluoroethylene (Gore-Tex) 8 mm in diameter, which is interposed between the portal vein and vena cava (Figure 5).

We recently reported a prospective, randomized trial comparing the use of large-diameter total shunts with that of small-diameter partial shunts.[36] Both shunts were 100% effective in controlling hemorrhage. Partial shunts preserved hepatopedal flow in 90% of patients and had a notably reduced incidence of encephalopathy. Long-term patency rates exceed 95%.

We recommend using small-diameter H grafts for patients with Child class A or B alcoholic cirrhosis and at least one previous episode of variceal hemorrhage.[37] Although this procedure has succeeded for the emergency control of bleeding and in patients with Child class C cirrhosis, the associated high mortality (around 50%) is unacceptable. In class C cirrhosis that cannot be improved by medical management, a rational alternative is TIPS followed by liver transplantation (see the next section). For acute life-threatening hemorrhage, the experience of the surgeon should determine the choice of shunt.

A New Procedure—Transjugular Intrahepatic Portacaval Shunt

Angiography has long been an important diagnostic method for planning elective surgical shunts. Recently, invasive angiographic techniques have been applied to the control of variceal hemorrhage. Transjugular intrahepatic portacaval shunt has been performed in many centers, and short-term data on uncontrolled, large series of patients are beginning to appear.[38,39] Initial enthusiasm has given way to cautious optimism and an effort to define more clearly the subset of patients most likely to benefit from the use of this technique.[40] The results of an uncontrolled series suggest that TIPS is particularly effective as a "bridge" to transplantation for patients with end-stage liver disease.[41]

The procedure is done by means of a percutaneous puncture of the right internal jugular vein. Structures are located by fluoroscopy and ultrasonography. Using a modification of the Seldinger technique, a guide wire is inserted into an intrahepatic branch of a hepatic vein. A needle is advanced over the guide wire through the substance of the liver into a nearby branch of the portal vein. The resulting tract is dilated with a balloon. An expandable stent of 8 to 10 mm in diameter is positioned to maintain patency of the communication between hepatic and portal veins (Figure 6). A patent portal vein is necessary for the performance of TIPS.

The advantages of TIPS include immediate portal decompression, the avoidance of general anesthesia, and a lack of intrusion into the portal hepatis.[42] Disadvantages include technical failure,[38,39,43] shunt stenosis or thrombosis in 30% to 50% of patients at one year,[39,43,44] with the possibility of rebleeding and other complications such as shunt migration or intra-abdominal hemorrhage. The rate of the latter complications is related to the experience of the interventionist, but stenoses and thromboses of the stents are thought to be due to neointimal hyperplasia. As the procedure continues to be refined, it is anticipated that the stenosis and thrombosis rates will improve.

Reported early mortality for emergency TIPS ranges from 30% to 56%.[39,43] The lower figure compares favorably with the approximately 50% operative mortality for emergency portacaval shunt, and the higher figure is not substantially worse. Early mortality for elective TIPS has been less than 10% in major series[39,43]; this is comparable to elective surgical shunts. Because a reporting bias is likely to exist with any new procedure (favorable results tend to be reported more often), prospective randomized trials are needed to determine the actual mortal-

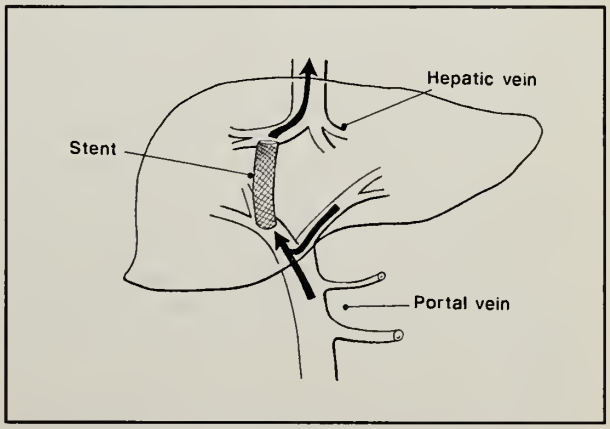

Figure 6.—*Transjugular intrahepatic portacaval shunt (TIPS)*: By percutaneous access to the jugular vein, an expandable stent is positioned within the liver parenchyma to achieve a functional connection between a branch of the portal vein and a branch of the hepatic vein. The arrows indicate the direction of blood flow. Portal flow is directed through the stent to the superior vena cava. For clarity, the inferior vena cava is not shown.

ity. Mortality data stratified by Child class will be particularly valuable.

One group has cautioned against uncritical acceptance of TIPS for all patients with variceal hemorrhage.[43] These authors suggest that TIPS is most appropriate for patients with Child-Pugh class C cirrhosis and those awaiting liver transplantation. They emphasize stabilizing the patient and using standard modalities for the control of hemorrhage—endoscopic sclerotherapy, splanchnic vasoconstrictors and balloon tamponade—before TIPS is done. Proper resuscitation beforehand and participation by experienced anesthesiologists during emergency TIPS may improve results in patients with acute hemorrhage.

Other Operations for Complications of Portal Hypertension

Esophageal Transection and Devascularization

Sugiura and Futagawa described a complex procedure for the control of variceal bleeding, consisting of dividing and reanastomosing the gastroesophageal junction, followed by suture ligating the remaining collaterals on the surface of the stomach.[45] Sugiura's original operation requires doing both a laparotomy and a thoracotomy. The goal of the procedure is to directly obliterate varices and to occlude their inflow through dilated collateral vessels. Outcomes with this procedure in Japan, where nonalcoholic cirrhosis is the prevailing cause of portal hypertension, generally have been excellent.[46] Experience outside Japan has been less consistent.[47] Rebleeding rates vary widely. Hospital mortality, as with shunt procedures, is related to the severity of underlying liver disease and to the urgency of the procedure. Substantial complications can include anastomotic leaks and stenoses. The rates of encephalopathy are uniformly low, around 5% to 10% overall.[46,47]

A less complicated modification involves simultaneous transection and reanastomosis of the distal esophagus using a surgical circular stapler introduced into the esophageal lumen through an incision in the stomach.[48] This can be combined with suture ligation of the left gastric vein. The aim is to interrupt inflow to the varices without obliterating them directly. In four controlled trials comparing esophageal transection with sclerotherapy, hospital mortality was similar, and early rebleeding was higher after sclerotherapy in three of the trials.[49-52] Late rebleeding is not prevented by esophageal transection. One of these trials also compared the use of transection with that of total shunts[52]; mortality was no different, and control of bleeding was better in the group receiving the shunts.

For patients for whom medical therapy fails, but who cannot be shunted (because of portal vein thrombosis, for example), esophageal transection and reanastomosis is a satisfactory option. Those with better residual liver function will have better outcomes.[53] In addition, this potentially lifesaving procedure may be done in an acutely bleeding patient by surgeons who lack experience with emergency portacaval shunts.

Splenectomy

Thrombosis of the splenic vein may result in bleeding from gastric varices arising from the short gastric veins. In these uncommon cases, splenectomy is the definitive treatment.[54] Polyvalent pneumococcal vaccine and counseling about the possibility of overwhelming postsplenectomy sepsis syndrome should be given. Portal hypertension-associated hypersplenism with thrombocytopenia is not an indication for splenectomy.[55]

Surgical Treatment of Ascites

The medical control of ascites requires salt and water restriction, drug therapy, and maintaining serum protein levels adequate to exert normal intravascular oncotic forces.[56] Spironolactone antagonizes the elevated circulating aldosterone levels associated with portal hypertension. Loop diuretics such as furosemide enhance the excretion of excess extracellular fluid, but necessarily cause intravascular volume depletion at the same time. Therapeutic paracentesis is used as an adjunct to these measures.

Therapy may be limited by various competing factors. Salt and water restriction can be difficult to enforce. When it succeeds, the resulting hypovolemia may predispose to renal insufficiency, especially when diuretics are given during a state of prerenal azotemia.[56] Hepatic protein synthesis may be impaired by the underlying disease. Frequent therapeutic paracentesis may exacerbate the depletion of serum proteins. Adequate dietary protein intake may worsen encephalopathy.

In circumstances where medical measures cannot control ascites, portacaval shunts may do so for patients who otherwise meet the indications for shunting.[57] Total portacaval shunts will decrease ascites substantially over time, although at a cost of worsened encephalopathy in about 40% to 50% of patients. Transjugular intrahepatic portacaval shunt may act hemodynamically as a total or partial shunt[38,39] and appears to decrease ascites, but it also increases the incidence of encephalopathy. The ultimate role of TIPS in treating ascites remains to be defined. Selective and partial shunts are not reliable for controlling ascites, although usually they do not worsen it and may reduce it in some cases.[30,58] Portacaval shunts for ascites should be offered only to patients with a history of variceal bleeding in addition to refractory ascites. The choice of shunt procedure may be influenced by the added goal of controlling the ascites.

For the specific control of ascites, two types of peritoneovenous shunts are available in the United States.[59] The LeVeen shunt consists of a silicone (Silastic, Dow Corning Corp, Midland, Michigan) conduit with a passive, pressure-actuated, one-way valve. One end is placed in the peritoneal cavity by a minilaparotomy. The shunt is tunneled subcutaneously to the neck where the other end is secured in the internal jugular vein. The Denver shunt is similar except that its one-way valve is placed over a rib where it can be actively pumped by external compression. Both shunts aim to immediately recirculate ascites

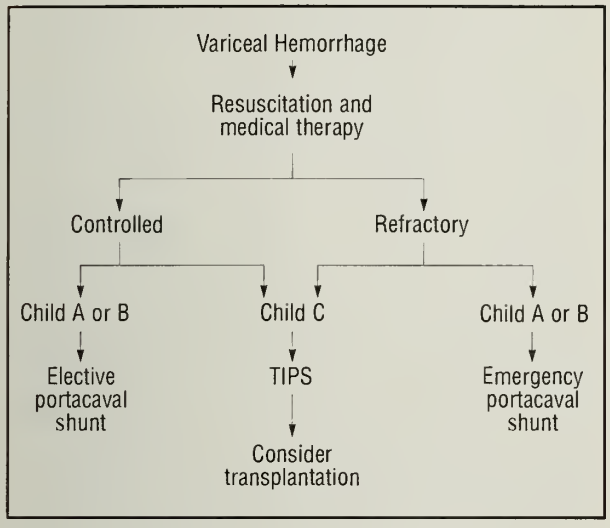

Figure 7.—An algorithm is given for the management of variceal hemorrhage. The urgency of a transjugular intrahepatic portacaval shunt (TIPS) will depend on whether or not hemorrhage can be controlled medically.

fluid into the vascular compartment. This is associated with a consumptive coagulopathy that may progress to disseminated intravascular coagulopathy.[60] Severe cases of coagulopathy are treated by ligation of the shunt. Other complications include congestive heart failure from volume overload, infection, venous thrombosis, and eventual occlusion.[61] In patients in whom the shunts work as designed, ascites is abolished, but the potential for variceal hemorrhage may be increased due to hypervolemia and coagulopathy. A large, prospective, randomized trial failed to show a survival benefit of the use of peritoneovenous shunt over medical therapy for massive ascites in alcoholic patients, although ascites was treated more effectively by surgical procedures.[62] As a last resort, peritoneovenous shunts may improve the quality of life for patients with refractory, disabling ascites but with considerable risk.

Liver Transplantation

Liver transplantation has become increasingly successful in recent years because of improvements in organ preservation, surgical technique, critical care, and immunosuppression.[63] Candidates for transplantation now may include alcoholic patients with end-stage cirrhosis. Transplantation for the treatment of alcohol-induced liver failure even in nonabstinent patients has been advocated by one prominent group because results are comparable to transplantation for other causes of liver failure, and their patients tend not to resume alcohol abuse after the transplantation.[64]

Indications for transplantation are not the same as those for portacaval shunt. Although the transplantation does correct portal hypertension, the goal of therapy is to restore hepatic function. Patients with variceal bleeding who have adequate hepatic reserve or reversible liver failure are shunted instead. Those with end-stage liver failure (manifested by persistent jaundice, encephalopathy, and inadequate synthetic capacity) are considered for transplantation.[65]

Once the need for transplantation is established, a patient undergoes an extensive medical and psychosocial evaluation to determine whether contraindications to transplantation exist. Absolute contraindications include sepsis, active substance abuse, a malignant neoplasm outside the liver, the failure of a second organ system, or the acquired immunodeficiency syndrome. Relative contraindications include noncompliance, intrahepatic carcinoma, advanced age, and multiple previous operations.[65] Portal vein thrombosis, until recently an important obstacle to transplantation, can now be dealt with using techniques to bypass or reconstruct the obstructed portal vein.[66] The requirement for immense financial resources and the serious nationwide shortage of organ donors may prove to be insurmountable barriers for many patients who might otherwise benefit from transplantation.

Patients who have undergone previous portacaval shunts may present technical challenges to a transplantation team. For this reason, it is important to weigh the likelihood of a future need for transplantation against the immediate need for controlling hemorrhage when choosing initial therapy for variceal bleeding. Mesocaval shunts, the distal splenorenal shunt, and TIPS are considered less likely to cause difficulty for a transplantation surgeon when compared with other shunt procedures.[67] Still, none of these is an ideal procedure in all circumstances, and decisions as to the preferred shunt operation must be made on an individual basis.[68]

Summary of Recommendations

Life-threatening variceal hemorrhage due to portal hypertension requires a rapid evaluation and aggressive resuscitation. Ideally, diagnostic measures and supportive treatment will be instituted simultaneously. Medical treatment will control acute bleeding in most patients. Decisions regarding definitive management then can be approached systematically. Factors such as the cause of portal hypertension, adequacy of hepatic reserve, possible candidacy for liver transplantation, and likely compliance with therapy can be assessed. Local skills will also influence management.

In the few patients whose hemorrhage proves refractory to initial therapy, emergency portacaval decompression should be done without delay. For patients with satisfactory hepatic reserve (Child class A and B), surgical portacaval shunt will arrest variceal hemorrhage with acceptable operative mortality. For those with end-stage liver disease (Child class C), TIPS followed by liver transplantation is indicated. Not all centers will offer these specialized procedures, and variations from this outline will often be justified by individual circumstances.

A simplified algorithm depicting our overall scheme for managing variceal hemorrhage is given in Figure 7. "Resuscitation and medical therapy" includes airway management, fluid resuscitation, the transfusion of blood products, pharmacotherapy, endoscopic control of bleed-

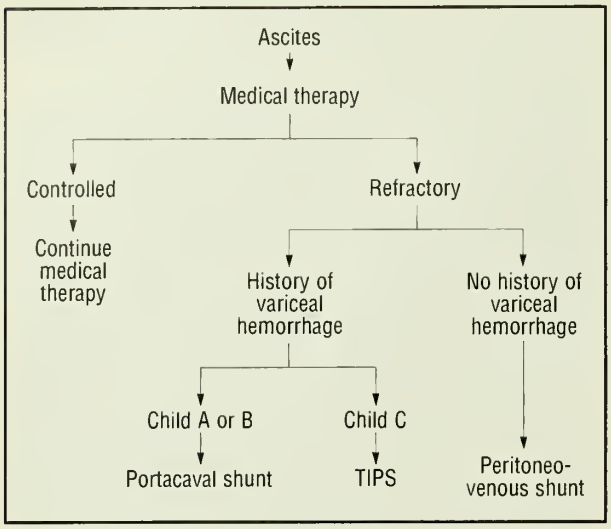

Figure 8.—An algorithm is shown for the management of ascites. Intractable ascites may be one of several factors suggesting the diagnosis of end-stage liver failure. For such patients, liver transplantation is the best therapy. TIPS = transjugular intrahepatic portacaval shunt

ing by sclerotherapy or ligation, and possible tamponade with the Sengstaken-Blakemore tube. It is reasonable to attempt endoscopic control of hemorrhage twice within a period of a few hours before declaring the failure of medical therapy and referring the patient for emergency surgical intervention. Resuscitative efforts must be vigorous and continuous, regardless of the therapy chosen. It is prudent to notify a surgeon (who may be asked to do an emergency procedure on short notice) early in the patient's hospital course.

Ascites is controlled with medical therapy—diuretics, salt and water restriction, and periodic paracentesis—in most patients. For those whose ascites proves refractory, surgical therapy may improve the quality of life. Patients with a concomitant history of variceal bleeding should be managed by portacaval shunt. This prevents future episodes of hemorrhage and controls ascites. Those who have never bled from varices may benefit from peritoneovenous shunting, so long as they are willing to accept the risks of bacterial peritonitis, congestive heart failure, intravascular coagulopathy, variceal bleeding, and shunt occlusion. Our simplified algorithm for the surgical treatment of ascites is shown in Figure 8.

End-stage liver failure is best treated by liver transplantation. For patients with sufficient resources who meet the indications and have no absolute contraindications, replacement of the liver is the definitive therapy for portal hypertension and its complications.

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Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

C. Gregory Jellinek, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association, and the summaries were prepared under the direction of C. Gregory Jellinek, MD, and the panel.

Melanoma—Current Concepts

In whites, melanoma represents one of the most rapidly increasing cancers and is the leading killer among all skin diseases, accounting for as much as 2% of the number of cancer deaths in the United States. By the end of the 20th century, the lifetime risk of melanoma for whites in the United States is forecasted to be 1 in 90. A direct relationship between UV radiation exposure and melanoma is strongly supported by current epidemiologic data. Studies on five continents have shown an inverse linear relationship between melanoma and latitude, with increasing incidence and mortality as one approaches the equator. Melanoma is less likely to develop in more heavily pigmented persons. The rate of tumor occurrence is 8 to 19 times greater in white Americans than in black Americans. Still, the exact role of UV radiation remains unclear because no animal model simulating clinical experience exists, and it is unclear what amounts and patterns of UV exposure are required to induce melanoma.

Grossly, melanomas typically vary in color and have irregular borders and raised or ulcerated surfaces. Any pigmented lesion with these features or that shows a change in gross structure should be examined histologically. Besides surgical biopsy, a detailed history and physical examination along with a chest radiograph and serum liver enzyme panel are the minimal steps in evaluating such a lesion.

The initial therapy for all primary melanomas should be surgical, although the extent of resection necessary to obtain regional control is continually being reevaluated. In situ tumor requires 0.5- to 1-cm margins of grossly uninvolved tissue. Tumors from 1 to 4 mm are adequately controlled with margins from 1 to 2 cm, the greater margins reserved for thicker lesions. Above 4 mm in thickness, margins of 3 cm have been recommended, but these recommendations are based only on nonprospective data. Reconstruction following ablative surgical procedures is generally straightforward, proceeding from primary closure through grafts and local or distant flaps, with special attention needed when dealing with the acral parts.

With adequate primary extirpation, local control is obtained in more than 95% of patients and regional control in 97% of patients. Lymphatic nodal lesions with obvious clinical involvement must be excised completely and anatomically. The treatment of occult disease in lymphatic drainage basins (elective lymphadenectomy) remains an area of continued controversy. Where the chance of occult disease is minimal, as in thin tumors (< 1 mm thickness), lymphadenectomy is deferred. A considerable number of patients with thick tumors (> 4 mm) will have microscopic spread to lymph nodes, and lymphadenectomy is therefore therapeutic. For patients with intermediate-size tumors (1.0 to 3.99 mm), the recently described technique of sentinel node biopsy may offer a method of selectively documenting occult nodal disease before extirpation. The technique has a reported false-negative rate of roughly 5%. The long-term effect on survival has yet to be determined.

Recurrent disease or intransigent tumors can be treated with re-excision, irradiation, or the isolated limb perfusion of chemotherapy. Re-excision is appropriate for limited recurrent or persistent disease. Isolated limb perfusion, with carboplatin, dacarbazine, or thiotepa, can also be used repeatedly to preserve limb function and ambulation and gain control of multiply recurrent localized disease, with a number of patients being disease-free for five to eight years.

Metastatic melanoma is associated with a poor prognosis, although the clinical course can be unpredictable. Isolated metastatic tumor should be resected. Parenteral chemotherapy and radiotherapy have not been found to increase the overall survival rate of most patients.

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Facial Fractures

FEW AREAS OF PLASTIC SURGERY have changed as rapidly as the management of complex facial fractures. Just over a decade ago, these patients were treated with a conservative "wait and see" attitude, and the subsequent deformities that developed were hard to correct. Those patients who did undergo surgical therapy early were treated with small incisions, minimal exposure of fracture segments, and fixation with wires or external devices, frequently yielding poor functional and aesthetic results. This conservative approach, with delayed operative repair, has evolved to an aggressive, early, one-stage approach. This evolution has been made possible by several developments, most notably the contributions of Paul Tessier of Paris, who is considered the father of craniofacial surgery. Tessier showed that it was possible to expose nearly the entire craniofacial skeleton through relatively hidden incisions and to "work" on the bone. This may consist of osteotomy and repositioning of a segment of bone to a more functional or aesthetic position or, as in the case of displaced facial bone fractures, repositioning the bone to its proper anatomic position.

Several principles have evolved to guide us in our care of patients with facial trauma. First, a precise anatomic diagnosis is imperative. The history and physical examination are supplemented by computed tomographic (CT) scans as indicated. The precision of CT is such that with both axial and coronal cuts, the fracture pattern can be precisely identified. The CT scan allows those patients to be selected who may not require surgical intervention and, for those who require surgical therapy, the precise planning of the operative procedure.

Through a combination of coronal, upper and lower eyelid, and intraoral incisions, nearly the entire craniofacial skeleton can be approached through subperiosteal dissection. Fracture segments are identified and reduced to their proper anatomic position. Inadequate exposure of fracture segments may result in inadequate fracture reduction and malpositioning, leading to a difficult-to-correct secondary deformity. Three-dimensional reconstruction to restore preinjury facial height, width, projection, and a functional occlusion is the goal.

After fracture exposure and anatomic reduction, the bones must be held in position during the healing phase. Internal fixation devices—tiny plates and screws, some less than 1 mm in thickness—are frequently used to stabilize the bony fragments. With the development of the principle of primary bone grafting, the incidence of secondary soft tissue scarring and contraction and associated deformities has been dramatically reduced. Bone grafts are used to replace missing or damaged bone or to correct contour deformities. Outer table cranial bone provides an excellent source in patients with craniofacial trauma.

As part of the goal of reestablishing the pretraumatic appearance, management of the soft tissue of the face is critical. Areas of abrasion are meticulously cleaned and debrided as necessary, and soft tissue lacerations are repaired anatomically. After subperiosteal dissection to expose the facial skeleton, most of the soft tissue attachments to the underlying skeleton are lost. It is important to resuspend the soft tissue envelope over the underlying foundation. This is accomplished by attaching with sutures the periosteum from the soft tissue envelope to the skeleton either directly to remaining periosteum or occasionally to plates and screws that were used for fixating fracture fragments. This will redrape the soft tissue envelope and prevent the soft tissue droop that in the past has been associated with wide exposure of complex fractures of the face.

The principles of the management of complex facial fractures continue to evolve. A more aggressive approach using craniofacial principles and techniques, including anatomic fracture fragment reduction, relatively rigid internal fixation with primary bone grafting as necessary, and definitive soft tissue management, seems to have dramatically diminished the incidence of secondary deformities associated with these devastating injuries.

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Role of Endoscopic-Assisted Plastic Surgery in Aesthetic Therapy

THE PROLIFERATION OF endoscopic procedures in the surgical specialties has been astounding. In general surgery, over a several-year period laparoscopic cholecystectomy has gone from a curiosity to the most commonly performed general surgical procedure. Today, virtually every field has found valid application for endoscopy based on the premise that these techniques diminish patient morbidity compared with "open" procedures. In no specialty is patient morbidity of more concern than in aesthetic plastic surgery.

The most common endoscopic procedure currently done by plastic surgeons is the brow lift. In its traditional form, this requires elevating a transcoronal flap (an incision across the top of the scalp from ear to ear) anteriorly to the level of the supraorbital rim with the resection of corrugator and procerus muscles, followed by the excision of excess brow skin. With the use of the endoscope, the forehead can be elevated in a subgaleal or subperiosteal plane by several small (1.5 to 2 cm) transverse or longitudinal incisions within the hairline. At the level of the orbital rim, the periosteal attachments of the brow are sharply released, and the depressor muscles are resected with grasping forceps while visualizing the supraorbital

and supratrochlear nerves. Galeal suspension is accomplished by plication sutures at the level of the skin incisions or by fixation to microscrews placed in the calvarium. Skin resection is generally not necessary.

The advantage of this technique is greater patient acceptance of the procedure. Early reports have indicated that endoscopic brow lifts are accompanied by diminished bleeding and swelling, less scalp anesthesia, and a less noticeable scar. In a review of 61 patients undergoing endoscopic brow lift, no important complications occurred, and results were equal to those with the open coronal approach.

The natural extension of this procedure, endoscopic face lift, is also gaining acceptance. Patient selection for this procedure is critical. Ideal candidates are younger (< 50 years of age) and have good skin tone without nasolabial folds or prominent malar fat pads. Patients with substantial skin redundancy are best served by standard rhytidectomy. The endoscopic dissection is accomplished in the subcutaneous plane in the lower half of the face and in a subperiosteal plane in the upper third of the face by two temporal and posterior mastoid incisions about 1.5 cm long. An intraoral buccal sulcus and lower blepharoplasty incision can be used. After wide undermining, the soft tissues are suspended by endoscopically tied knots to the temporalis fascia and periosteum. The neck can also be treated using endoscopy or by direct vision through a submental incision.

Several other procedures, including abdominoplasty and breast augmentation, are currently being studied for their applicability to endoscopic-assisted dissection, and the list will undoubtedly continue to grow. Surgeons should view the current wave of enthusiasm for endoscopic plastic surgery with a note of caution, however. As with most new medical advances, the indications and applications are likely to be extended unnecessarily initially. Not until further experience with these techniques is reported should endoscopic manipulation in plastic surgery become routine.

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Chemical Peels in Plastic Surgery

CHEMICAL PEELS have gained widespread acceptance in the treatment of aging faces. Used appropriately, peels have proved effective in treating actinic damage, including fine wrinkles, pigmentary abnormalities, and dryness. Superficial acne scarring also responds favorably.

Many chemicals are available for facial peeling, including phenol, trichloroacetic acid (TCA), and the α-hydroxy acids. All act by varying degrees of cellular destruction of the epidermis and papillary dermis, producing consistent histologic changes. These include homogenization of the dermal collagen structure, the diminution of melanin granules in the basal epidermis, and an increase in elastic tissue. This results in a leveling of superficial irregularities including fine wrinkles.

Phenol, the most commonly used agent, is a derivative of coal tar. Popularized by the work of Baker and Gordon in the 1960s, it is generally used at a concentration of 50%. Higher concentrations result in increased toxicity without additional therapeutic benefit. Infrequently, phenol can cause cardiac arrhythmias, and full-face phenol treatments should not be done without continuous electrocardiographic monitoring and intravenous access. This complication is more common when more than 50% of the face is treated in less than 30 minutes.

Phenol is mixed in a formula consisting of 3 ml of phenol, 2 ml of water, 8 drops of soap, and 3 drops of croton oil. After applying, many practitioners place a light layer of antibiotic ointment to prevent evaporation and enhance wound healing.

Trichloroacetic acid is used at concentrations varying from 15% to 50%, with higher concentrations producing deeper peels. Unlike with phenol, there is no systemic toxicity, and the response to the agent is not all or none. The results obtained are highly dependent on prepeel skin preparation, including washing with soap, degreasing with acetone or ether, and applying a keratinolytic agent such as Jessner's solution (resorcinol, salicylic acid, and lactic acid) to disrupt the stratum corneum. Failing to prepare the skin adequately can result in a spotty peel. The method of application can enhance results. Repeated application or vigorous rubbing of the acid into the treated area increases the depth of penetration.

The α-hydroxy acids have enjoyed a recent burst of popularity among lay practitioners of skin care. All are derived from the fermentation of natural food sources such as fruit, with the first documented use occurring in ancient Egypt when sour milk (lactic acid) was applied to the face to enhance beauty. At low concentrations (usually less than 10%), these substances are found in over-the-counter skin preparations. Their effect is based on reducing the cohesion of the keratinocytes, producing desquamation and epidermolysis. They have a good safety profile but limited clinical efficacy. The most commonly used fruit acid, glycolic acid, works to loosen the buildup of dead skin cells. Over a series of treatments in a six- to eight-week period, this exfoliation process results in softer and smoother skin. The duration of effects is being studied. Currently, only plastic surgeons and dermatologists are doing TCA and phenol peels, as well as α-hydroxy peels of a 50% to 70% concentration.

After a facial peel, patients can expect crusting to occur in the first three to five days. During this time, they are instructed to apply topical antibiotic ointment. By 10 to 14 days, the crusting has resolved, with the underlying skin taking on an erythematous appearance. Moisturizing lotion is used liberally to prevent secondary drying and

cracking. Patients are instructed to stay out of direct sunlight for four to six months because a substantial number of melanocytes are removed during the peeling process. In the event of sun exposure, all patients should wear a sunscreen with a sun protection factor of 15 or greater.

Complications are most frequently related to pigment changes. In patients with darker complexions, hyperpigmentation may develop over treated areas, which, although usually transient, can be permanent. This can be prevented or minimized by applying hydroxyquinone, a bleaching agent, before or after the peel. In addition, the erythema seen in all chemically peeled skin may persist for several months. Involution of the redness is accelerated by the application of a steroid cream, if needed. The most serious complication is hypertrophic scarring or full-thickness skin loss from a peel that extends too deeply. This can usually be avoided by reducing the concentration, the application pressure, or the duration of the peeling agent and by avoiding skin recently undermined by rhytidectomy or blepharoplasty. When used appropriately by experienced professionals, complications are rare, particularly with TCA and α-hydroxy acid peels.

No discussion of peeling agents would be complete without mentioning topical retinoic acid (tretinoin). Although not used as a peeling agent itself, it is frequently used for prepeel skin conditioning. Its mechanism of action is unknown, but it is thought to involve diminishing the cohesiveness of epithelial cells, stimulating mitosis, and causing a thickening of the dermis and compaction of the epidermis. Although approved by the Food and Drug Administration for the treatment of cystic acne only, it is currently in broad use for the long-term correction of fine facial wrinkling.

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Breast Reconstruction

A RECONSTRUCTIVE OPTION is available for almost any woman undergoing a mastectomy. Reconstruction is an important step in a woman's recovery from cancer or other breast disease. Reconstruction promotes a woman's sense of well-being, wholeness, and recovery. This option should be explained to her before mastectomy and even before she makes a decision regarding mastectomy versus lumpectomy. Women who undergo reconstruction at the same time as a mastectomy do better emotionally postoperatively. At any time following a mastectomy, however, even many years later, a woman may consider and undergo reconstruction.

Reconstruction should not be postponed because of the possibility of further treatment, such as chemotherapy. Chemotherapy cannot start until the patient recovers from the mastectomy. Recovering from the reconstruction, therefore, if done at the same time as the mastectomy, does not delay the start of chemotherapy. In addition, it has been shown that breast reconstruction does not interfere with the early detection of recurrence of breast carcinoma.

In general, breast reconstruction can be divided into two types, using either autologous tissue or implants. Reconstruction involving implants first requires the use of a tissue expander. This is placed at the time of the initial mastectomy, under the pectoralis muscle. The tissue expander is then slowly inflated to stretch the mastectomy flaps. Once the flaps have been expanded to a size larger than the opposite breast, a second procedure is done to exchange the expander for a permanent saline or silicone implant. The second procedure can be done on an outpatient basis, using either local or general anesthesia.

A reconstructed breast using an implant is usually higher, firmer, and rounder than the opposite breast. The ideal patient for this type of reconstruction has small, nonpendulant breasts. It is also an excellent method for patients requiring bilateral mastectomy, as symmetry can be easily achieved.

Silicone implants are available for women undergoing reconstruction, under strict guidelines and surveillance of the US Food and Drug Administration. Saline implants also offer an excellent reconstruction for many women undergoing this procedure. In some patients with a thin skin-and-muscle covering over the implant, a rippling can occur in the upper pole of the reconstructed breast, resulting in an unnatural feel.

The second type of reconstruction involves using a patient's own tissue. Most commonly, the skin and fat of the abdomen can be elevated on one of the underlying rectus abdominis muscles and transferred to the chest area to reconstruct the breast mound. This method is called a TRAM (transverse rectus abdominis myocutaneous) flap. It generally results in a superior breast reconstruction, giving a natural feel and appearance. It also dispenses with the need for implanted materials and can be accomplished in one stage. These procedures can also be used for bilateral reconstruction because both rectus muscles can be elevated, each carrying half of the skin and fat of the lower abdomen. When reconstruction is done using only one rectus muscle, little or no abdominal strength is lost. Women who undergo bilateral reconstruction involving the use of both rectus muscles can sometimes experience abdominal and back weakness, however. Currently, the TRAM flap is the preferred procedure in postmastectomy reconstruction.

The latissimus muscle can also be transferred from the back. This usually does not provide enough tissue for an adequate breast mound and often requires the use of a supplemental implant. This is a good method for patients who are obese, smoke cigarettes, or who have had multiple abdominal operations (all of which can compromise the blood supply of flaps) and, therefore, are not candidates for a TRAM procedure. The tissue expander with

implant or latissimus muscle with implant should be considered as a reconstructive option for these patients.

In general, reconstruction of the nipple-areolar complex is accomplished, if the woman wishes, three months after her initial reconstruction. Nipple-areolar reconstruction is delayed until after chemotherapy is completed. Local tissue is used to create the nipple, and a skin graft is harvested from either the abdominal scar (TRAM incision) or the lower groin area. Following healing, the nipple-areolar complex is tattooed to match the color of the opposite side.

Although a perfect match cannot be made with the normal breast, in most cases a breast can be created that comes close in form and appearance and allows a woman to wear a normal bra and clothing.

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Skin Substitutes

BURN WOUNDS remain the most common condition requiring skin substitutes, but skin substitutes have also been used to treat dermatologic disorders such as giant hairy nevi excision, chronic skin ulcers, and pressure sores.

Skin substitutes vary from simple inert dressing materials to engineered biomaterials and cultured cells. The plethora of skin substitutes available today reflects each product's inability to meet all of the requisites of an "ideal skin." The most appropriate coverage must be tailored to the type of wound.

Wounds that retain dermal elements, or partial-thickness wounds, have deep progenitor elements within adnexa of the skin and therefore retain their capacity to regenerate. These wounds are readily treated with occlusive dressings that maintain a moist environment, reduce pain, promote re-epithelialization, and allow patient mobility during the healing process. The most commonly used occlusive dressings are Opsite and Xeroform gauze. Other moisture-retaining dressings, which some consider synthetic skin substitutes, remain a treatment option and include hydrocolloids and the newer hydrogels. For wounds requiring this type of dressing, however, synthetic substitutes function simply as expensive dressings. A note of caution with the use of hydrogels is that they lack the ability to exclude bacteria, and this dressing may favor the growth of gram-negative bacteria.

More severe wounds may have full-thickness injury, may be dirty and require debridement, or full-thickness loss may have occurred during debridement. Without the use of autologous tissue or a skin substitute, they typically close with profound contraction and scarring. Dead tissue should be excised as soon after injury as possible to limit bacterial colonization. A skin substitute should then be used to aid healing, act as a barrier to infection, or most important, to buy time for granulation tissue development, repeated harvest, or autologous cell culture.

Allograft is the current treatment of choice for skin substitution. Depending on the quality (viability) of its preparation and the patient's wound-induced immunosuppression, engraftment does take place and can provide prolonged coverage. Tissues, for historic reasons, are not regulated by the US Food and Drug Administration (FDA). As a result, the quality may be highly variable and often not available.

The quest for a cheap, available, and reliable new material is still active. Biobrane II (Dow-Hickham) is now the only biosynthetic device approved for use as a skin substitute by the FDA. It is a porcine type I collagen-coated nylon mesh (for tissue ingrowth) with a thin silicone (moisture barrier) backing. Although its certified use is for the long-term coverage of wounds left by the debridement of full-thickness burns, its successful use as a donor-site dressing to speed healing and to provide comfort has been reported. In full-thickness burn wounds, the Biobrane engrafts and, on removal, the silicone sheet separates, leaving the collagen base in the wound. The synthetic substitutes are far less resistant to wound contamination than either autologous or allogeneic skin grafts. With infection, complications range from a loss of adherence of the device to invasive sepsis and death.

Cultured autologous epithelium represents an important advance in the area of skin substitutes. This is the only permanent skin substitute and necessitates biopsy and culture of autologous keratinocytes. The burn wound is excised to expose viable tissue and requires a substitute for coverage while the clonal expansion of cultured cells takes place—usually about three weeks. Once available, the cultured epithelial grafts are placed on the granulating wound bed. This has resulted in a 20% to 70% take as compared with a 95% take for traditional autograft. Cultured keratinocyte autograft is able to form anchoring fibrils without a dermal component present, but this can take from 6 to 12 months. This interim graft instability accounts for the complications of sloughing, blistering, scarring, and wound site contraction. This phenomenon is attributable to the lack of a dermal component that, if present, promotes early anchoring fibril formation. The current state of the art in autograft keratinocyte culture depends on good allograft take. Instead of removing the entire allograft, just the epithelium is removed with a burr or dermatome to retain the engrafted nonantigenic dermal component as a base for the cultured cells. This improves the take in the areas of retained dermis to about 95%.

Inconsistent allograft take has led to the current direction of research and clinical trials with the application of a highly processed allodermis or the use of dermal substitutes in conjunction with cultured epithelial grafts, to increase graft take and achieve more rapid integration and healing.

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Removal of Gang-Related Tattoos

TATTOOING is commonly used among subculture groups such as youth gangs to permanently identify their members. After someone has made the decision to leave a gang, his or her physical graffito remains a stigma. Many former gang members need to move to a different city to avoid the risk of rival gang members threatening their lives. Getting a job is also a problem for those young people, as prospective employers hesitate to hire persons with gang-related tattoos on visible areas such as the hands, neck, and face. In desperation, many former gang members have resorted to home remedies for tattoo removal, such as burning them off with a cigarette or pouring acid on them.

Until recently, medical tattoo removal provided equally poor results. Dermabrasion results in severe hypertrophic scarring. Excision leaves scars and, unless the tattoo is small, requires multiple serial excisions, skin grafts, or tissue expanders. Chemical tissue destruction with caustic chemicals such as tannic acid or silver nitrate burns the skin. In the early 1960s, with the introduction of medical lasers, it was hoped that precise necrosis of tissue containing pigment would eliminate scarring. Thermal tissue destruction with the argon, carbon dioxide, and tunable dye lasers, however, also resulted in unacceptable scarring.

The Q-switched (wide pulse) lasers of the neodymium:yttrium-aluminum-garnet (Nd:YAG), alexandrite, and ruby varieties have provided technology that results in minimal to no scarring. Each requires several treatments. The Q-switched ruby laser results in hypopigmentation in more than 50% of patients; this is usually transient, but may be permanent. It is also slow because of the limited number of pulses per second. The Q-switched Nd:YAG laser works more effectively because it can emit as many as 10 pulses per second. The 1,064 wavelength is longer and increases dermal penetration. There is less skin textural change than with the ruby laser and no hypopigmentation. The Nd:YAG laser is most effective with black ink and works well on dark-skinned persons. The 532 wavelength is good for red ink. All of these lasers break the ink up into many small pieces and stimulate the body's own macrophages to "clear" the ink. The ink is taken up by these cells. Gang-related tattoos tend to be mostly homemade, and the ink is found at varying depths in the dermis. This is in contrast to professional tattoos that are usually deeper and more uniformly placed in the dermis. Most of the gang tattoos are black ink; the commonly seen dark green color of tattoos results from metabolism of the black ink. Current laser tattoo removal requires several treatments at intervals of six to eight weeks; most gang tattoos are removed after four to five treatments; professional tattoos usually require more. Laser tattoo removal is safe, effective, and results in almost no complications.

The new lasers are costly—about $80,000 and up. Tattoo removal can cost several thousand dollars, and often former gang members cannot afford it. Many communities around the country are setting up tattoo removal clinics with physicians volunteering their time and hospitals and clinics volunteering space and assistance. Purchasing the laser is usually the obstacle, but as the interest grows, public officials and private corporations are helping out. Proper patient selection is most important; removing tattoos should be just one step in the rehabilitation of these young people to productive society.

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Alerts, Notices, and Case Reports

Arterial Thrombosis in Ulcerative Colitis

Transcatheter Thrombolytic Therapy

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THROMBOEMBOLISM has been recognized as a rare but serious complication of inflammatory bowel disease since six cases were first described in 1936.[1] Case studies and reviews since then have emphasized the poor prognosis associated with thrombosis. Two thirds of cases have been due to deep venous thrombi or pulmonary embolic events.[2] Some reports have discussed the diagnosis and treatment of venous thrombosis, but effective management of extensive arterial thrombosis associated with inflammatory bowel disease has not been previously described. We report the occurrence of bilateral lower extremity arterial thrombosis in a patient recently diagnosed with inflammatory bowel disease. Circulation was restored with the transcatheter intrathrombic administration of urokinase (Abbokinase; Abbott Laboratories, North Chicago, Illinois).

Report of a Case

The patient, a 27-year-old woman, was admitted to the University of California, Davis, Medical Center (Sacramento) because of crampy abdominal pain, watery diarrhea, and tenesmus. She reported that for the past five days leg cramps had developed after she walked short distances, and on the evening before admission, her left leg became numb and she was unable to bear weight on it. She also had some numbness in the fingers of her right hand. Five months before admission, flexible sigmoidoscopy and biopsies of the sigmoid colon showed ulcerative colitis. She was initially treated with sulfasalazine, but was switched to high-dose oral prednisone for improved control. At the time of admission to the medical center, she had been taking 60 mg of prednisone each day. She was also taking birth control pills.

On physical examination, she was afebrile, with a diffusely tender abdomen. Her right index finger was noted to be cyanotic, cool, and numb distally. Her peripheral pulses were intact, without bruits. She had decreased sensation to light touch in both feet, worse on the left.

Laboratory analysis revealed a hemoglobin concentration of 77 grams per liter (7.7 grams per dl), a hematocrit of 0.24 (24%), a leukocyte count of 9.2×10^9 per liter (9,200 per mm^3), and a platelet count of 402×10^9 per liter (402,000 per mm^3). The serum concentrations of sodium, potassium, chloride, bicarbonate, creatinine, urea nitrogen, alkaline phosphatase, alanine aminotransferase, γ-glutamyltransferase, and total bilirubin were within normal limits. The albumin concentration was 26 grams per liter (2.6 grams per dl). The prothrombin time was 11.5 seconds, which is within the normal range. Her stool was guaiac-positive.

For her colitis, the patient was treated with a regimen of 80 mg per day of prednisone and intravenous cyclosporine. A course of nifedipine was started for presumed Raynaud's phenomenon affecting the right index finger. Flexible sigmoidoscopy was done to 40 cm. From 20 to 40 cm, several large, widely spaced ulcers with patchy erythema were seen. The intervening mucosa appeared normal. Gastrointestinal blood loss was treated by transfusion. Autoimmune vasculitis was excluded by negative tests for antinuclear antibodies and rheumatoid factor; the C3, C4, and protein S levels were normal. A protein C level was 68% (74% to 137% of normal human plasma).

Further evaluation was conducted for a hypercoagulable state, specifically the primary antiphospholipid syndrome. This revealed phosphatidylserine immunoglobulin (Ig) antibody IgG, IgM, and IgA levels all elevated greater than 2 standard deviations. Also, the anticardiolipin antibody IgG level was 21 phospholipid units per ml (normal, <15). Three days after admission, the patient had the sudden development of severe left leg and left foot pain and an inability to flex or extend the left foot or toes. Physical examination revealed her left foot to be pulseless and cold. The patient's steroid and birth control drugs were discontinued because they may have contributed to a hypercoagulable state.

She was referred to the interventional radiology service for consultation. Biplane aortography with bilateral lower extremity runoff was done and showed normal aortic and visceral vascular anatomy. Small thrombi were demonstrated in the right internal iliac artery and in distal branches of the right deep femoral artery (Figure 1-A). There was occlusion of the right infragenicular popliteal artery (Figure 1-B). Thrombus was demonstrated in the right posterior tibial, anterior tibial, and peroneal arteries. No flow was seen past the right mid-calf (Figure 1-B). The left side showed total occlusion of the distal common femoral artery with thrombus seen in the deep left femoral artery (Figure 1-A). Eventually segmental reconstitution of the distal superficial femoral

(Lengle SJ, Nadler P, Jordan GW: Arterial thrombosis in ulcerative colitis—Transcatheter thrombolytic therapy. West J Med 1995; 162:543-547)

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Figure 1.—Before treatment, **A**, subtraction angiogram of the pelvis and upper thighs shows thrombus in the right internal iliac artery **(large solid arrow)** and distal branches of the right deep femoral artery **(small solid arrows)**. There is occlusion of the left common femoral artery and thrombus in the left deep femoral artery **(open arrows)**. **B**, Cut-film arteriography shows thrombus in the anterior tibial, common tibioperoneal, peroneal, and posterior tibial arteries **(open arrows)**. There is occlusion of the right infragenicular popliteal artery **(small solid arrow)**. No flow is seen past the left popliteal artery at the level of the knee **(large solid arrow)**.

artery and occlusion of the supragenicular popliteal artery occurred. No flow was demonstrated past the level of the knee joint on the left side (Figure 1-B).

The patient underwent transesophageal echocardiography and duplex Doppler evaluation of the lower extremities. There was no evidence of peripheral deep venous thrombosis, intracardiac anatomic abnormalities, or intracardiac thrombus; therefore, a provisional diagnosis of in situ arterial thromboembolism was made. Consultation was obtained with staff from the Department of Vascular Surgery. Because of the multiple sites of thrombosis and the possibility of a vasoplastic component, a trial of catheter-directed intrathrombic thrombolytic therapy was attempted. Should this fail, surgical thrombectomy would then be attempted.

Treatment

Because of a progressive loss of motor function and sensation, we initially concentrated on treating the patient's left leg. Thrombolytic therapy was begun using the pulse-spray pharmacomechanical thrombolytic technique as described elsewhere.[3,4] This was accomplished by passing a guide wire into the thrombus in the common and superficial femoral arteries. This was exchanged for a multiple–side-hole catheter. A mixture of 250,000 IU of urokinase in 9 ml of normal saline solution and 1 ml of 5,000 IU of heparin per milliliter was prepared. Repeated small-volume (0.2 to 0.4 ml), high-pressure injections of concentrated urokinase solution were made into the occluding thrombus. Once flow was established into the occluded vessel, the catheter was secured in place. The infusion technique of urokinase delivery was then initiated.[5,6] A mixture of 250,000 IU of urokinase in 62.5 ml of a solution of 5% dextrose in water was infused at 4,000 IU per minute (about 60 ml per hour). This was maintained for 1 hour, followed by 2,000 IU per minute (30 ml per hour) for 2 hours and then 1,000 IU per minute (15 ml per hour) for 16 hours. Systemic anticoagulation was maintained with the intravenous administration of heparin. We attempted to maintain a partial thromboplastin time between a range of 60 and 80 seconds during her course of thrombolytic therapy. Nifedipine administration was continued to treat any vasospastic component of her thrombotic state. Fibrinogen levels were closely monitored to evaluate for a systemic lytic state. On the second day of thrombolysis directed toward the left lower extremity, the fibrinogen level decreased from 2.3 to 0.8 grams per liter (226 to 78 mg per dl). The urokinase infusion was discontinued, heparin therapy was continued, and fresh frozen plasma was transfused. Her fibrinogen level increased to 1.9 grams per liter (192 mg per dl). The patient underwent follow-up arteriography the next morning. Moderate residual thromboemboli remained, and therapy directed at the left lower extremity was extended for about 72 hours with intermittent arteriography to evaluate for the progression of thrombolysis. After a total of 3.5 million IU of urokinase was administered, the left posterior tibial and dorsalis pedis pulses returned, and the left leg became warm and viable.

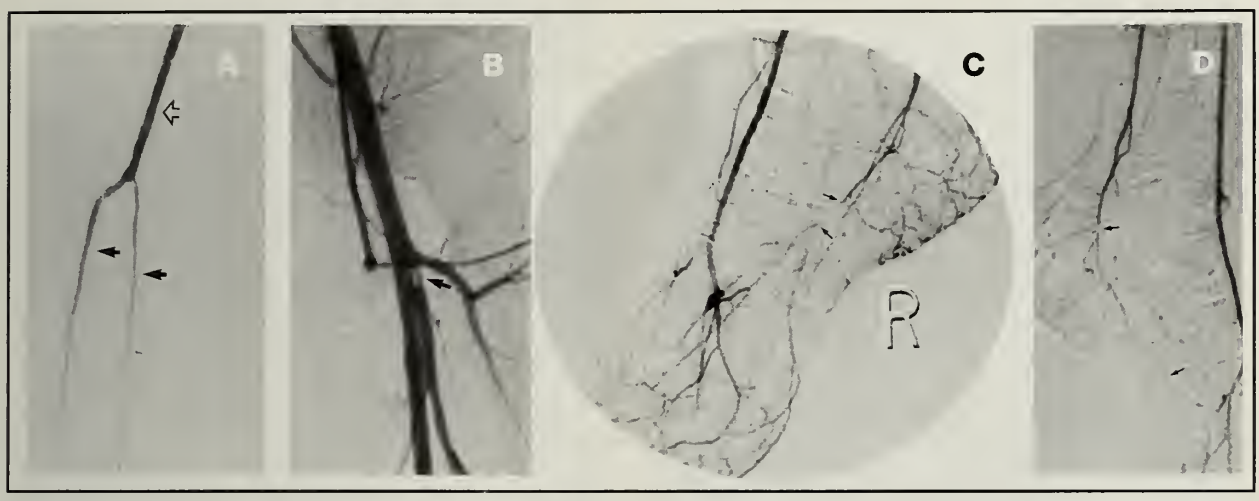

Figure 2.—After treatment, **A**, digital subtraction angiogram of the right lower extremity shows patency of the right popliteal (**open arrow**) and posterior and anterior tibial arteries (**closed arrows**). There is persistent occlusion of the peroneal artery. **B**, Digital subtraction angiogram of the left proximal femoral region shows a small amount of nonoccluding thrombus in the descending branch of the left deep femoral artery (**closed arrow**). The common femoral, deep femoral, and superficial femoral arteries are otherwise patent. **C**, Digital subtraction angiography of the right foot shows occlusion consistent with small thrombi in the plantar arch of the right foot (**small closed arrows**). **D**, Digital subtraction angiography of the left foot shows evidence of small thrombi within the plantar arch and distal posterior tibial artery (**small closed arrows**).

The right leg began showing evidence of worsening ischemia with some loss of sensation on the day that transcatheter therapy was completed on the left. A multiple–side-hole infusion catheter was positioned in the right popliteal artery, and the guide wire was passed down the trifurcation vessels. Using both pulse-spray and infusion techniques, a total of 2.25 million IU of urokinase was administered to the right leg over approximately 36 hours. The patient showed pronounced improvement in the perfusion of the right leg, with the return of near-normal sensation and motor function. Systemic anticoagulation was maintained with heparin throughout the course of thrombolytic therapy. The partial thromboplastin time was maintained in the 60- to 80-second range. Antiplatelet therapy was withheld with the hopes of minimizing gastrointestinal blood loss. Also, the thought was that if hemorrhagic complications recurred, heparin and urokinase therapy could be rapidly reversed, whereas platelet inactivation would require additional transfusions.

Because of the development of hematochezia and bleeding into the right forearm from previous radial arterial punctures for blood gas measurements, thrombolytic therapy was discontinued on hospital day 6. Fortunately, the patient's lower extremity perfusion had improved bilaterally, and she was no longer at risk for limb loss. After the development of bright red bleeding per rectum on hospital day 6, her hematocrit dropped from about 0.40 to 0.33 (40% to 32.6%) and remained stable. No further blood transfusions were required. Because of the patient's previous endoscopy showing several large widely spaced ulcers in her sigmoid colon, this was presumed to be the source of bleeding, and no further colonoscopy was done. After the discontinuation of thrombolytic and anticoagulation therapy, the patient's gastrointestinal bleeding resolved.

Final arteriographic evaluation of the left leg (on hospital day 4) and the right leg (on hospital day 6) showed widely patent vasculature with minimal thrombus seen in the left deep femoral artery (Figure 2-B), distal left posterior tibial arterial branches, and left plantar arch (Figure 2-D). There was persistent occlusion of the right peroneal artery (Figure 2-A) and a small amount of thrombus in branches of the plantar arch of the right foot (Figure 2-C). Anticoagulation therapy was changed from heparin to warfarin sodium, and she was discharged after four weeks of hospital stay with good pulses distally and improved lower extremity strength.

The patient is currently doing well 1½ years after her episode of arterial thromboembolism. She has been on long-term warfarin therapy without recurrent symptoms of lower extremity ischemia.

Discussion

In 1936 a total of 18 cases of thrombophlebitis or arterial thrombosis occurred among 1,500 cases of chronic ulcerative colitis.[1] A series of 7,199 patients with inflammatory bowel disease were observed from 1970 to 1980 at the Mayo Clinic (Rochester, Minnesota), and thromboembolic complications were found in 92 (1.3%).[7] Of these 92 cases, only 7 involved peripheral arterial thrombosis.

The cause for the association of thromboembolism and inflammatory bowel disease is not clear. Bargen and Barker suggested several mechanisms: stasis from bed rest, severe infection, local damage to the large iliac veins due to neighboring peritonitis, and propagation from small rectal veins.[1] Other investigators have found increases in coagulation factors V and VII and fibrino-

gen and decreases in antithrombin III.[8] Still others have noted decreased platelet survival, thrombocytosis, and spontaneous platelet aggregation.[9] One author linked coagulation with activation of the monocyte-macrophage system and the release of fibrinopeptide A.[10] As noted, this patient had borderline elevated levels of anticardiolipin IgG antibody. In another report, the risk of thromboembolic complications was reviewed in patients with inflammatory bowel disease.[11] Of 20 patients studied, 6 had slightly increased titers of anticardiolipin antibodies. Overall, 14 of the 20 patients with inflammatory bowel disease studied had at least one change in hemostasis measurements considered as risk factors for thrombosis. An association between anticardiolipin antibody and disease was also noted in a case report.[12] Anticardiolipin antibodies may be an underlying cause of the association of thromboembolism and inflammatory bowel disease.

Although arterial thrombosis is a relatively rare complication of ulcerative colitis, its occurrence has been associated with a poor prognosis.[1,7,13,14] The need for early diagnosis is important because effective therapy is now available. Of 60 cases at autopsy, thromboembolism was cited as the cause of death in 7.[14] In another report, thrombi and emboli were present in 14 of 43 patients dying of inflammatory bowel disease,[1] and 23 of 92 patients (25%) died during a thromboembolic complication.[7] Two groups of patients had a substantial risk of mortality: those with recurrent deep venous thrombosis and pulmonary emboli associated with exacerbations of their disease, and those with septicemia that develops as a complication of severe inflammatory bowel disease or a surgical procedure.

The most effective treatment of thrombosis occurring in a patient with inflammatory bowel disease has not been established. Streptokinase was reportedly successful in the treatment of extensive venous thrombosis.[9] Until now, however, in the few cases of arterial thrombosis described in the literature, patients have been treated with surgical embolectomy. Consultation with our vascular surgical colleagues resulted in a decision to first attempt transcatheter thrombolytic therapy, to be followed by surgical embolectomy should transcatheter therapy fail. Because of the several sites and extensive degree of thrombosis, numerous arteriotomies and surgical thromboembolectomies would have been required. We thought that the less invasive transcatheter therapy would have a good chance for success and did not preclude surgical thromboembolectomy should transcatheter therapy fail. Our experience indicates that thrombolytics may also be useful for extensive as well as multiple arterial thromboses.

The overall risk of complications of thrombolytic therapy ranges between 3% and 28%, with the incidence of major complications ranging between 3% and 11.5%.[15,16] The most common complication of thrombolytic therapy is hemorrhage. Other possible complications include distal embolization, pericatheter thrombosis, reperfusion syndrome requiring fasciotomy, or amputation.[15] Attempts were made to administer short-duration pulse-spray urokinase whenever possible to decrease the systemic effects and the complications associated with urokinase therapy. The risk of reintroducing additional gastrointestinal bleeding in our patient was discussed at length with her and her referring medical team. The patient and the treating physician staff agreed that therapy would be continued until limb salvage had been accomplished or complications necessitating discontinuation of therapy were encountered. Her fibrinogen levels were maintained above 1.0 grams per liter (100 mg per dl), and the platelet count was kept above 100×10^9 per liter (100,000 per mm^3). Close monitoring was maintained in the medical intensive care unit. The patient's gastrointestinal bleeding and the bleeding into the right forearm occurred at a point in her treatment when limb salvage had been accomplished. Therefore, we felt that the risk of continued urokinase therapy was outweighed by the risk of bleeding.

For some patients, long-term anticoagulation has been successful in preventing recurrent thrombosis.[17] Warfarin therapy, however, presents additional risks for patients who have a predisposition for gastrointestinal hemorrhage. Partial obstruction of the vena cava with an umbrella or clip has been advocated as a way to prevent pulmonary emboli in patients with venous thrombosis.[7] In some cases, colectomy may be indicated, as this has been shown to prevent the recurrence of the systemic complications of inflammatory bowel disease.[18]

The transcatheter intrathrombic administration of urokinase provides an attractive alternative to surgical embolectomy for the treatment of arterial thromboembolic complications of inflammatory bowel disease.

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Unilateral Femoral Pistol-Shot Sounds
A Clue to Aortic Dissection

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THE FEMORAL "PISTOL-SHOT SOUND" is a short, loud, snapping sound heard with the stethoscope over both femoral arteries in some patients with severe aortic regurgitation. These sounds are identical to the Korotkoff sounds elicited in the brachial artery during blood pressure measurements. Although femoral pistol-shot sounds are usually bilateral, we describe the case of a patient with unilateral pistol-shot sounds who was found to have a type B aortic dissection (without aortic regurgitation) involving the artery immediately proximal to where the sound was discovered.

Report of a Case

The patient, a 69-year-old man with hypertension and an ectatic thoracic aorta, was transferred to the Seattle (Washington) Veterans Affairs Medical Center in March 1989 with severe chest pain. Examination revealed a blood pressure in both arms of 160/92 mm of mercury, a pulse of 76 beats per minute, a midsystolic apical murmur, and symmetric pulses in the neck and upper and lower extremities. There was no diastolic murmur. Auscultation of the right femoral artery was remarkable for a short, loud, snapping sound with each pulse (pistol-shot sound). No pistol-shot sound was heard over the left femoral or brachial arteries.

(McGee SR, Adcox M: Unilateral femoral pistol-shot sounds—A clue to aortic dissection. West J Med 1995; 162:547-548)

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A chest x-ray film revealed a massively dilated aortic arch and descending thoracic aorta. Aortography showed a type B aortic dissection beginning at the left subclavian artery and extending at least to the level of the renal arteries, possibly as far as the right common iliac artery. No aortic regurgitation was seen. The patient did well with conservative management that consisted of a regimen of metoprolol tartrate, isosorbide dinitrate, and nifedipine.

Four years later, a magnetic resonance scan confirmed that the dissection had extended at least to the level of the right common iliac artery (Figure 1).

Discussion

Femoral pistol-shot sounds usually result from the sudden expansion and tensing of the walls of the femoral arteries during systole,[1] and consequently, they are associated with the wide pulse pressures seen in patients with aortic regurgitation and in normal persons after receiving peripheral vasodilators, such as tolazoline hydrochloride.[2] The sounds are analogous to the loud, snapping notes heard when a sail or parachute suddenly fills with wind. The quicker the vessel dilates, the louder the note, and in patients with aortic regurgitation, the intensity of the pistol-shot sound correlates with the height of the pulse pressure[3] and the change in pressure over time (dP/dt) of the pulse.[2]

Abrupt expansion of other large vessels may produce similar sounds, such as the venous pistol-shot sound (sudden dilation of the jugular and femoral veins by the systolic venous wave of severe tricuspid regurgitation),[4] the presystolic snapping jugular sound (abrupt tensing of the jugular vein by a giant A wave in patients with right atrial hypertension),[5] the double femoral sound (found in patients with severe pulmonary hypertension, the first component being venous from right atrial systole and the second being arterial from left ventricular systole),[6] and the Korotkoff sounds. Korotkoff sounds occur because the artery underneath the constricting cuff collapses and suddenly opens with each beat when sphygmomanometer pressures are between the patient's systolic and diastolic blood pressure (the artery opens because the systolic pressure is greater than the cuff pressure; it collapses because the cuff pressure is greater than diastolic pressure).[1,7] When the cuff pressure falls below the patient's diastolic pressure, the artery no longer collapses and the sound disappears.

Previous large studies that reviewed the clinical findings of patients with aortic dissection fail to include a description of the unilateral femoral pistol-shot sound,[8-10] although in one patient with a type A dissection extending to the right internal iliac artery, a "double, metallic, clicking sound," synchronous with each pulse, was heard over the abdominal aorta for a period of 12 hours.[11]

The unilateral pistol-shot sound in our patient appeared immediately downstream from the distal end of his type B dissection (the right common iliac artery). When the sound was first noted, our patient was not

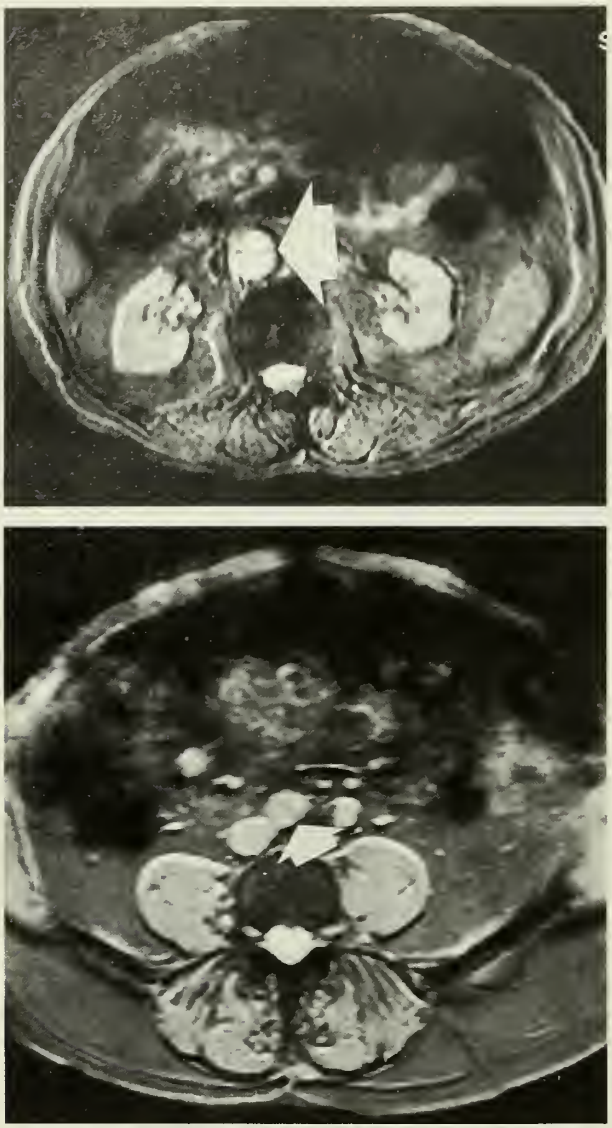

Figure 1.—A flow-sensitive magnetic resonance scan (gradient recalled echo) reveals an area of low signal intensity (representing the intimal flap) in the infrarenal abdominal aorta (**top, large arrow**) and the right common iliac artery (**bottom, small arrow**). Rapidly flowing blood is bright with this technique, thus demonstrating flow in both the true and false lumens.

receiving vasodilating medications for blood pressure control. We speculate that the sound may have resulted from sudden systolic tensing of the dissected intimal flap, a mechanism that is consistent with the other pistol-shot sounds mentioned earlier. This mechanism may also provide an explanation for the double clicking sound previously described in a case of aortic dissection,[11] with the dissected intimal flap tensing twice with each beat (initially with flow through the true lumen and subsequently with slower flow in the false lumen). Such duplication of flow through true and false lumens has been previously described to produce a double pulse.[12] An alternative explanation for the sound in our patient, that it resulted from blood distending the false lumen to pressures exceeding the diastolic blood pressure, thus causing the collapse of the true lumen with each beat (analogous to Korotkoff sounds), seems unlikely in view of the patient's magnetic resonance scan showing free flow through the true and false lumens.

Even with experienced practitioners, aortic dissection is initially misdiagnosed in almost 40% of patients.[10] Moreover, femoral artery pulse deficits are found only 2% to 14% of the time.[9,10] The presence of a unilateral femoral pistol-shot sound in patients with chest pain and normal femoral pulses is another peripheral arterial finding that may be helpful in making this difficult diagnosis.

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Hepatotoxic Reaction to Chloroquine Phosphate in a Patient With Previously Unrecognized Porphyria Cutanea Tarda

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THE ADMINISTRATION of chloroquine to a patient with porphyria cutanea tarda can cause a dramatic reaction marked by fever, malaise, and porphyrinuria accompanied by transient hepatotoxicity. This reaction is well known in the dermatologic literature, but is barely mentioned in a standard internal medicine textbook discussion of porphyrias.[1] Commonly used drug references

(Liu AC: Hepatotoxic reaction to chloroquine phosphate in a patient with previously unrecognized porphyria cutanea tarda. West J Med 1995; 162:548-551)

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mention only the potential of chloroquine phosphate to "exacerbate" porphyria without describing the actual reaction seen.* Since the initial reports of chloroquine's effects in patients with porphyria cutanea tarda published in the 1950s,[4-6] there have been few case descriptions of chloroquine reactions in patients previously undiagnosed with this disorder. We report a case in which a hepatotoxic reaction developed in a patient with mild, unrecognized porphyria cutanea tarda after chloroquine phosphate was given as malaria prophylaxis.

Report of a Case

The patient, a 61-year-old woman, presented with fever and red urine for two days. She had recently been seen in preparation for a three-week trip to Central America. A week before her planned departure, the patient took a single 500-mg dose of chloroquine phosphate as malaria prophylaxis. The following day she had mild nausea without vomiting, a fever to 39.5°C (103°F), and noted slightly reddish urine. By the next day when the patient presented for evaluation, her fever had lessened, but the urine was now dark red. She did not have dysuria, urinary frequency, urgency, or abdominal pain; she continued to feel warm, but had no other specific complaints.

The medical history was remarkable for a hysterectomy for fibroids with incidental appendectomy in 1973; de Quervain's thyroiditis in 1980; and the development of menopausal symptoms in 1983, prompting the initiation of estrogen replacement therapy. There was no history of hepatitis or blood transfusion.

In 1988 the patient had presented with fine blistering of the fingers. A topical steroid was prescribed without improvement during the use of the medication; the blistering later resolved. Later in 1988 the patient was seen because of facial hypertrichosis. Thyroid function test results and androgen levels were within normal limits. She then underwent electrolysis to remove the unwanted facial hair, and there was no recurrence of hypertrichosis. The family history was noncontributory. The patient's only medication was conjugated estrogens (Premarin), 0.9 mg daily. She did not use alcohol. She had no known allergies.

On examination, the blood pressure was 140/84 mm of mercury and temperature 37.2°C. The skin appeared normally pigmented, without vesicles, bullae, hypertrichosis, sclerodermoid changes, or stigmata of chronic liver disease. There was no hepatosplenomegaly, and the remainder of the physical examination findings was unremarkable. The urine was burgundy red but dipstick-negative for occult blood, with 0 to 3 erythrocytes. Dipstick test was also negative for protein, glucose, and bile; a urine myoglobin test was negative. The hematocrit was 0.46 (45.6%), and a leukocyte count was 14.8 $\times 10^9$ per liter (14,800 per mm^3). The serum aspartate aminotransferase level was 45.4 μkat per liter (2,724 U per liter; reference range, 5 to 40 U per liter), and the lactate dehydrogenase level was 26.2 μkat per liter (1,576 U per liter; reference range, 60 to 200 U per liter). Serum alanine aminotransferase level was 41.1 μkat per liter (2,468 U per liter; reference range, 0 to 21 U per liter). The total bilirubin level was normal at 18 μmol per liter (1.1 mg per dl; reference range, 0.2 to 1.2 mg per dl); alkaline phosphatase, 1.9 μkat per liter (115 U per liter; reference range, 30 to 115 U per liter); and γ-glutamyl transpeptidase, 0.55 μkat per liter (33 U per liter; reference range, 0 to 65 U per liter). Serum haptoglobin, albumin, electrolytes, creatinine, and glucose levels were normal. Serologic tests for hepatitis A and B were negative. Testing for hepatitis C antibody was not done.

Chloroquine was discontinued. The patient's transaminase levels fell, and her fever resolved, although the urine remained red. The patient traveled to Central America as planned. On her return, she reported that the red urine color had resolved after about ten days. At this time, the diagnosis of porphyria was considered. The skin remained free of vesicles, bullae, or sclerodermalike changes, although some redness had developed on sun-exposed areas during the patient's travel. Urinary porphyrin levels were obtained by spectrofluorometric assay. The 24-hour urine uroporphyrin level was 699 nmol per day (581 μg per 24 hours; reference range, 0 to 50 μg per 24 hours) with a coproporphyrin level of 519 nmol per day (340 μg per 24 hours; reference range, 80 to 250 μg per 24 hours), consistent with porphyria cutanea tarda. The serum ferritin level was 143 ng per ml (reference range, 14 to 186 ng per ml for postmenopausal women). A skin biopsy of an area of redness at the forearm showed inflammation but no vesicles, bullae, or sclerodermoid changes consistent with porphyria cutanea tarda.

TABLE 1.—*Causes of Red Urine**

Occult blood-positive
Erythrocytes
Free hemoglobin
Myoglobin
Occult blood-negative
Bilirubin
Melanin
Porphyria
Ingestions
Beets, blackberries
Drugs
Laxatives—phenolphthalein, danthron, cascara sagrada
Metronidazole
Phenazopyridine HCl
p-Aminosalicylate (only on contact with hypochlorite)
Quinacrine HCl
Rifampin
Sulfasalazine (Azulfidine)

HCl = hydrochloride

*From Physicians' Desk Reference,[2] Berman,[7] Jacobs et al,[8] Glucksman,[9] and Bell.[10]

*References 2 (pp 2086-2087) and 3 (pp 905-909).

Discussion

The most striking aspects of this patient's presentation were her dark red urine and pronounced liver function abnormalities, occurring despite her relatively normal clinical appearance. Red urine can be caused by hematuria or a variety of other disorders (Table 1).[2,7-10] Most of these disorders were ruled out by the patient's initial laboratory evaluation. Porphyria was considered, but erroneously rejected as a diagnosis because acute, severe hepatocellular abnormalities are not a feature of any of the porphyrias.[11] A review of the effect of chloroquine in porphyria cutanea tarda provided the necessary information leading to the correct diagnosis of this disorder.

The porphyrias are a group of disorders caused by enzymatic defects in heme synthesis, leading to the accumulation of nonfunctional by-products called porphyrins. Porphyria cutanea tarda is the most common of the porphyrias, with an estimated incidence of 1 in 25,000.[11,12] In this disorder, which can be inherited or sporadic, a deficiency of uroporphyrinogen decarboxylase leads to the accumulation of uroporphyrin and 7-carboxylic porphyrin.[11] Photoactivation of these porphyrins then occurs on skin exposure to light in the Soret band, which lies between visible violet and ultraviolet light. This photoactivation is thought to lead to the formation of singlet oxygen and eventually to tissue damage. Thus, sun exposure leads to a phototoxic reaction characterized by vesiculobullous lesions; increased skin fragility and facial hypertrichosis are also typical of porphyria cutanea tarda. Hyperpigmentation and scleroderm-oid skin changes may also be seen.[11,13]

The acute attacks of abdominal pain seen in other hepatic porphyrias are absent.[11,14] Sporadic porphyria cutanea tarda may be triggered by alcohol overuse, estrogen use, or exogenous iron. It has also been observed in nonalcoholic liver disease, including chronic hepatitis B and C, systemic lupus erythematosus, and a variety of other disorders, including human immunodeficiency virus infection.[13-16] In addition, toxins such as hexachlorobenzene can cause the disorder by suppressing the activity of uroporphyrinogen decarboxylase.[12] Distinct from this toxin-induced form is "pseudoporphyria," in which skin changes identical to those seen in porphyria cutanea tarda occur without a disturbance in porphyrin metabolism. Pseudoporphyria has been described following the use of tetracyclines, naproxen, furosemide, nalidixic acid, and amiodarone, as well as in patients having hemodialysis and in persons using sun beds.[12,13,17-19]

The diagnosis of porphyria cutanea tarda is established by the presence of characteristic skin lesions and biochemical abnormalities. It is distinguished from other porphyrias by the presence of persistently elevated levels of uroporphyrin, with lesser degrees of coproporphyrin elevation; other porphyrins are also excreted in both urine and stool.[11] The urine color may be normal under visible light or appear red to brown if large amounts of porphyrins are present; examination under Wood's light reveals pink to red.[13] Skin biopsy specimens show subepidermal bullae with dermal papillae at the base. Serum aminotransferase levels may be persistently elevated, usually in relation to underlying conditions such as alcoholic liver disease.[20] Liver biopsy specimens often show siderosis with varying degrees of chronic inflammation and cirrhosis.

The treatment of this disorder begins with the avoidance of known precipitating factors such as alcohol, exogenous iron, and estrogens. In some cases, this is the only treatment needed.[21] Phlebotomy is the best-established treatment; it reduces urinary porphyrin concentrations and leads to the regression of skin lesions, probably by depleting hepatic iron stores.[13]

Chloroquine has also been used in the treatment of porphyria cutanea tarda; the intensity of treatment varies from "high-dose" therapy using 500 mg of chloroquine daily to "low-dose" treatment with 125 mg twice a week. Low-dose therapy is associated with a less acute toxic reaction. Administering chloroquine to a patient with porphyria cutanea tarda, particularly in high doses, can result in massive porphyrinuria due to the formation of a drug-porphyrin complex that is excreted in the urine.[22,23] With this reaction, fever, malaise, abdominal pain, and dramatically increased levels of aminotransferase are typically seen. The hepatotoxicity and constitutional symptoms associated with this reaction are usually self-limited and may be followed by a lengthy remission.[22,23] The mechanisms by which hepatotoxicity and subsequent remission develop are not known, but have been postulated to be due to the selective destruction of those mitochondria most responsible for porphyrin overproduction.[22] Complications are rare, though a single death has been reported of hepatic failure after the accidental administration of a single 1,250-mg dose of chloroquine for porphyria cutanea tarda.[24] Liver biopsy done in patients treated with chloroquine may show no change from baseline or may show hepatic cell necrosis.[25]

Our patient's fever, nausea, and red urine were typical of the chloroquine reaction seen in this disorder. Although the patient had no active skin lesions when she presented for travel prophylaxis, the history of vesicular lesions and facial hypertrichosis was consistent with the disorder. In this patient, the likely precipitant for the development of porphyria cutanea tarda was estrogen replacement therapy; she was not using alcohol or iron supplements, had no history of other illnesses associated with porphyria, and her skin lesions developed after she began estrogen replacement. The patient's uroporphyrin level, although lower than that seen in most patients with symptomatic porphyria,[20] was sufficiently elevated to confirm the diagnosis, even though this measurement was obtained well after her gross porphyrinuria had resolved.

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Editorials

Listen, Ye Legislators, Our Children Need You!

The Nation's poison control centers are in critical financial condition and several are on the brink of extinction. . . . Poison control centers across the country are closing their doors or dramatically curtailing services because of budget cuts. . . . In fact, only about half of all US residents have access to poison control centers that meet national quality standards.

REPORTED BY US HOUSE OF REPRESENTATIVES, OCTOBER 1994[1]

Poison control centers are widely recognized for their 24-hour telephone consultations for poisonings, about 60% of which involve unintentional ingestions by toddlers. Just as important are the consultations for suicidal adults, drug-abusing teens, hazardous materials bystanders, day care providers and school nurses, occupational health nurses, emergency medical technicians and paramedics, pregnant women with questions about drug or chemical safety, elderly patients with drug interaction queries, emergency physicians, pediatricians and intensivists managing acute poisonings, veterinarians, and even transplant surgeons evaluating potential organ donors.

Consultations are rendered in certified centers by highly trained, experienced health professionals who are required to achieve certification as specialists in poison information by passing a national examination. Medical backup is provided for challenging cases by the centers' medical and clinical toxicologists. An on-site library is maintained at each certified center, with hundreds of reference books, tens of thousands of journal articles, and extensive compendia of consultants, all supplementing the major source of information: the CD-ROM database POISINDEX (Rumack BH, Spoerke DG: POISINDEX® Information System. Englewood, Colorado, Micromedex, Inc).

As demonstrated by Kearney and co-workers in this issue,[2] poison control centers are cost-effective. Health economist Ted Miller, PhD, of the National Public Services Research Institute told Congress that every dollar spent on poison control services saves at least $7.75 in medical spending. This savings is comparable to that attained from immunizations.[3] Poison control centers, using highly sophisticated staff and frequent follow-up, are able to safely manage 75% of poison exposures at home. As a result, unnecessary emergency department visits, ambulance transports, and hospital admissions are prevented. Moreover, knowing the service is free, users do not hesitate to seek telephone guidance early, allowing rapid intervention when needed, appropriate and timely first aid, and prompt selection of patients who would benefit from more aggressive management. Undoubtedly morbidity is lessened as a result of this early intervention and the correct selection and rapid deployment of first-aid and decontamination procedures.

Poison control centers also play an essential part in poison prevention. Brochures, presentations, media spots, and news stories are used to educate the public. Poisoning surveillance is also key to successful prevention efforts. The American Association of Poison Control Centers compiles data on 1.8 million cases of poison exposures reported to participating poison centers annually in its Toxic Exposure Surveillance System (TESS). Using these computerized data, new or unusual hazards are detected. As a result of the alerting of regulatory agencies and industry, unusually hazardous products are reformulated, repackaged, or banned before additional needless injury or death occurs. Although Blanc and associates note in this issue the underreporting of adult poisoning fatalities to poison centers (especially drug abuse cases and narcotic or sedative overdoses),[4] the use of poison center data in poison prevention focuses on pediatric deaths and severe pediatric poisonings, an area where the TESS data are robust, representative, and timely.[5]

Of 86 poison control centers currently operational in the United States, only 40 meet the minimum quality standards promulgated by the American Association of Poison Control Centers. These 40 centers currently serve 55% of the US population, leaving nearly half of the US population with compromised or inadequate poison control services, predominantly as a result of profound fiscal limitations. Moreover, even the certified centers spend considerable effort scrambling for funds, thus diverting toxicologic expertise away from service, training, and surveillance to activities to sustain the center such as lobbying and fund-raising. Indeed, the certified center that I direct, the National Capital Poison Center in Washington, DC, is now facing its third threatened closure in a year, and despite community pleas for support, there is still no sign of long-term stable funding. Unfortunately, for many poison centers, brinkmanship has become the necessary but perilous road to survival, leaving its toll on staff retention and impairing center operations.

Poison control centers save lives. They save money. But they *cannot* be effective, *cannot* minimize poisoning morbidity, and *cannot* eliminate unnecessary health care costs without stable support. The issue is straightforward, eminently logical, and nonpartisan. Why are our legislators not listening?

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Whither Sarcoidosis?

We dance around in a ring and suppose,
But the Secret sits in the middle and knows

"Secret Sits"
ROBERT FROST

During the last quarter of the 19th century, Jonathan Hutchinson was one of the best-known medical consultants in London. An astute clinical observer, he was an outstanding combination of surgeon, dermatologist, ophthalmologist, syphilologist, internist, and expert on leprosy. In 1877, in his *Illustrations of Clinical Surgery*, he described the case of a 58-year-old man with large, purple, scaly, irregular, nontender skin lesions, arthritis, and chronic renal disease. Most medical historians believe that Hutchinson's patient suffered from what we now call sarcoidosis.[1]

Now, more than a century after Hutchinson's first description, sarcoidosis has emerged as a multisystem disorder characterized by the presence of noncaseating granulomata in the affected organs. Sarcoidosis has a high prevalence rate in Scandinavian countries, England, Ireland, North America, and Japan, but it is less frequent in Central and South America, mainland China, and Africa.[2] Despite the worldwide occurrence of sarcoidosis, the cause of the disease remains obscure and the understanding of its pathogenesis confounding and controversial. Attempts to elucidate its cause have been disappointingly thwarted by the lack of an animal model and the failure to identify the antigen. For practicing clinicians, the current status of knowledge of sarcoidosis has been reviewed by Asha N. Chesnutt, MD, in this issue of the *Journal*.[3]

The histopathologic hallmark of sarcoidosis is a well-defined round or oval granuloma made up of compact, radially arranged epithelioid cells with pale-staining nuclei. Lymphocytes may be found within the granuloma, but they are usually seen at the periphery.[4] The giant cell of the sarcoid granuloma is of the Langhan's type in which the nuclei are arranged in an arc or a circular pattern around a central granular zone. Caseation is absent, but minor degrees of fibrinoid necrosis may be seen, particularly in larger granulomas. Asteroid, Schaumann's, and Hamasaki-Wesenberg bodies are inclusion bodies frequently found within the epithelioid and giant cells; none of the inclusion bodies are, however, specific for sarcoidosis. The structure of the granuloma is an example of a perimeter defense commonly seen in many infectious and noninfectious disorders caused by various bacterial, fungal, viral, protozoan, parasitic, and mineral antigens. On the other hand, in sarcoid granulomas, no identifiable agent has ever been convincingly demonstrated.

Although the nature of the alien agent that causes noncaseating granuloma remains hidden, sophisticated immunologic, molecular biologic, and bronchoalveolar lavage techniques have given us a road map of the events that lead to granuloma formation. Sarcoid granuloma in the lungs appears to be an exaggerated immune response to an inhaled agent of low solubility and degradability.[5] The first step in the pathogenesis of sarcoidosis is the presentation of an unknown antigen(s) by macrophages bearing increased expression of major histocompatibility class II molecules to T cells of Th 1 type. This results in T-cell proliferation and activation. These activated T cells release a number of cytokines, including interleukin-2, monocyte chemotactic factors, macrophage migration inhibition factor, and leukocyte inhibitory factor.[6] Interleukin-2 activates and expands various clones of T lymphocytes, causing alveolitis. The monocyte chemotactic factor attracts monocytes from blood into the lungs. Other mediators such as macrophage migration inhibitory factor influence the trapped monocytes that are ready to transform into epithelial cells and modulate the formation of a granuloma. The granuloma formation and associated helper ($CD4^+$) T-lymphocyte alveolitis may lead to substantial alveolar injury. At this time, when the lung is the site of a tremendous outpouring of lymphocytes, the peripheral circulation shows a $CD4^+$ T-cell lymphopenia resulting in the depression of cutaneous delayed-hypersensitivity reactions.

Why does granuloma formation spontaneously subside in most patients, whereas in a few it progresses to fibrosis? Perhaps the two processes are not closely related. There is some evidence, however, that interferon gamma produced by Th 1 lymphocytes causes an increase in platelet-derived growth factor containing β subunits (PDGF-β) from macrophages.[7] Platelet-derived growth factor-β is chemotactic and a potent stimulant for fibroblasts, the main effector cell in the fibrotic response. Other cytokines that are chemoattractants for fibroblasts include transforming growth factor-β and matrix proteins. The mechanisms accounting for the increased production of matrix proteins—laminin, fibronectin, collagen peptides, elastin-derived peptides—are unknown.

We come back to the central question: What instigates the granuloma formation? From time to time we have incriminated *Mycobacterium tuberculosis* and atypical mycobacteria, but without much success.[8] Recently investigators demonstrated an increase in γ-δ cells in blood and lungs in sarcoidosis.[9] The T cells that bear γ-δ receptors are also prominent in leprosy, leishmaniasis, mycobacterial proteins, and heat-shock proteins. They suggested that one of these factors initiated the immune response that expanded into multisystem sarcoidosis.[9] Following the lead, many other investigators have used the polymerase chain reaction to detect mycobacterial DNA in clinical specimens from patients with sarcoidosis. *Mycobacterium tuberculosis* DNA was found in half of the sarcoidosis patients.[10] The findings are being hotly contested by other groups who did not find any mycobacterial DNA in bronchoalveolar lavage or tissue cells in sarcoidosis.

Many years ago it was suggested that sarcoidosis was caused by a transmissible agent.[11,12(p20)] Recently disseminated granulomatous inflammation developed in two patients without sarcoidosis who received heart transplants from donors who had sarcoidosis.[13] Granulomas have also occurred in heart and lung allografts in patients with sarcoidosis who received heart and lungs from nonsarcoidotic donors. These observations raise the possibility of a transmissible causative agent. Furthermore, the agent(s) remaining sequestered in the body is able to withstand aggressive immunosuppression and is capable of attacking transplanted lungs that have normal ventilation and perfusion.[14] If, indeed, there is a transmissible agent, where does it reside? Interestingly, a group of patients with sarcoidosis who had liver transplants for sarcoidosis or other causes of liver disease showed regression of the multisystem disease.[15] Did sarcoidosis subside in these patients because of immunosuppression or because of the removal of the diseased liver, the storehouse of the causative agent?

It is widely accepted that there is a sarcoid diathesis or constitution, but no definite genetic factors relating to the cause have so far been detected. The disease is clearly a worldwide phenomenon. Numerous contributing factors, including occupation, hobbies, pets, alcohol, tobacco, place of residence, family history, and use of drugs, have been analyzed, but no relationship has been found. It is relevant that the disease mostly affects persons between 20 and 50 years in age. Are these mobile, healthy, working people at a constant risk of inhaling an agent that is present universally? Is there another unidentified virus lurking around? The search continues.[16]

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Portal Hypertension—The Surgical Pendulum

THE PENDULUM HAS swung to and fro as to the role of surgical management for portal hypertension since Nicolai Eck first advocated his portacaval fistula. Eck's justification to use this shunt in humans was based on an 87% mortality in dogs. His bravado was rapidly countered by Pavlov's systematic assessment of the risks of liver failure with the deprivation of portal venous flow to the liver. A flurry of surgical activity in the early 20th century was characterized by Vidal's "forced" shunt and attempts at partial decompression by Morison's omentopexy.[1] Poor results led to abandoning the use of surgical therapy until the 1940s when a group at Columbia-Presbyterian Medical Center (New York, NY) popularized total portal systemic shunting. Initial enthusiasm, based on excellent control of variceal bleeding, soon waned when randomized trials documented the side effects of total portal diversion.[1] Surgeons sought a better way to manage variceal bleeding by selective variceal decompression[2] and extensive devascularization procedures[3] in the 1970s. Although popularity for these operations largely disappeared in the 1980s under the acclaim of sclerotherapy, by the late 1980s and 1990s, liver transplantation has swung the pendulum once more towards surgical therapy for some patients.[4] In addition, the realities of bleeding through sclerotherapy have brought back some of the previous surgical approaches in good-risk patients who do not need transplantation.

In their excellent review of surgical options in the management of portal hypertension in this issue of the journal, Collins and Sarfeh carefully outline the goals and outcomes of the various surgical possibilities.[5] How does a physician really decide what to do with a patient who presents with variceal bleeding? Clearly, variceal bleeding is one of those sentinel events in medical practice that requires full evaluation and definitive management decisions. Let us examine this question in a little more detail.

Acute Variceal Bleeding

Acute variceal bleeding is currently managed by endoscopic sclerotherapy. A new challenger, however, somatostatin or its analogue octreotide, is gaining popularity, with two randomized trials in acute bleeding documenting equal efficacy to sclerotherapy.[6,7] To practitioners who see few patients with variceal bleeding and who do sclerotherapy only occasionally, these data support the

use of octreotide (50 μg per hour) as a reasonable alternative. The popularity of the use of balloon tamponade has diminished, and its use should only be considered if a patient fails to stabilize with somatostatin or sclerotherapy, and even then only be used as a temporizing measure either to transport the patient or to arrange an alternative treatment modality.

I would take issue with the authors in advocating an emergency portacaval shunt for a patient in whom sclerotherapy for acute variceal bleeding fails. Transjugular intrahepatic portacaval shunt (TIPS) provides a less invasive alternative in such patients who are invariably high operative risks, and it provides portal decompression without an operation. Currently most centers accept this as an established role for TIPS.

Is there a role for emergency surgery within six hours of admission for variceal bleeding? A recent randomized trial provides data in support of this and, indeed, has led to a call for the further evaluation of this approach.[8,9]

Patient Evaluation

Patient evaluation is the key to making definitive treatment choices in a patient stabilized from an acute variceal bleed. The first question to be answered is whether the patient has end-stage liver disease that can only be managed by transplantation. If that is the case and the patient is otherwise an appropriate candidate for transplant, the choice is clear. At the other end of the spectrum, early identification of a patient with an extrahepatic cause for portal hypertension and a normal liver is important in further management of that patient. More difficult to sort out are the patients with cirrhosis with some impairment of hepatic function, but in whom the episode of variceal bleeding makes it difficult to judge the true severity, activity, and likely natural history of underlying liver disease.

Prevention of Rebleeding From Varices

Surgical decisions in the 1990s are not made in isolation, but as part of a team approach to total patient care. Once a patient is stabilized from an acute bleeding episode and has been evaluated, the surgeon has two questions to address:

• Is the patient now or at some time in the future likely to be a candidate for liver transplantation? If the patient has end-stage disease at this time and is a suitable candidate for transplantation, he or she should be transplanted. If the patient has advanced liver disease and is likely to come to transplantation in the next three to four years, the surgeon is less likely to advocate an alternative operative procedure, but would rather manage that patient with sclerotherapy, TIPS, or both. If the patient has a disease that may bring the patient to transplantation in the next five to ten years but has adequate hepatocellular reserve at this time, the decision may be that an alternative procedure such as a selective or partial shunt may provide good management for that patient for at least five years.[10,11] Such patients remain candidates for transplantation if and as their liver disease progresses.

A difficult patient is one with advanced disease but contraindications to transplantation, such as active alcoholism or substantial other-system disease. The management of variceal bleeding in such a patient may encompass any of the therapeutic modalities outlined in the current review.[5] Equally important, however, is to try and correct any associated concurrent underlying problems, as a proportion of these patients may ultimately become transplantation candidates.

• Which of the nontransplantation options provides the best surgical management? There is no single answer to this, but, rather, factors such as disease cause, portal venous anatomy, the availability of local skills, and the preference of the patient and surgeon weigh in this decision. There are advantages and disadvantages to each of the surgical therapies outlined. Total shunts control bleeding well, but the diversion of portal flow from a cirrhotic liver is associated with accelerated liver failure and a higher incidence of encephalopathy. Partial shunts and selective shunts have a lower incidence of hepatic failure and encephalopathy and control bleeding equally as well as total shunts. These are probably the most popular approaches at this time. Devascularization procedures have a higher risk of rebleeding but do not interfere with portal perfusion and liver function.[12]

In the mid-1990s, the pendulum has swung back in favor of surgical intervention for some patients with portal hypertension. Clearly the major surgical procedure in this field is liver transplantation, but for patients in whom there is preserved hepatic function in the face of variceal bleeding, other alternatives provide a reasonable approach for patient management.

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Correspondence

Ultrasonographic Diagnosis of Abdominal Aneurysm by Emergency Department Physicians

To the Editor: Ultrasonography offers untapped potential to improve the practice of emergency medicine. Painless, noninvasive, and without inherent risks or side effects, ultrasonography is a powerful and dynamic tool used for diagnosis and to facilitate invasive procedures. Currently used chiefly by radiologists, cardiologists, obstetricians, gynecologists, and vascular surgeons, it is well suited for emergency physicians as well.[1,2]

Over the next three to five years, it is anticipated that the diagnostic use of ultrasonography, as done by emergency physicians, will be the standard of care. The American College of Emergency Physicians has adopted a position statement supporting the immediate availability of emergency department ultrasonograms on a 24-hour-a-day basis. Many emergency medicine residency programs are now including ultrasound training in their curricula.

Unfortunately, many emergency department physicians are meeting resistance to the introduction of ultrasonography into their personal scope of practice. Radiologists, in particular, have shown a reluctance to endorse nonradiologists independently performing or interpreting ultrasonograms in the emergency department.

One key issue is the urgency of the examination. Emergency physicians think that, for certain patients, a 30- to 45-minute delay while awaiting the arrival of an on-call technician is unacceptable. Included in this group would be patients with an abdominal aortic aneurysm, a ruptured ectopic pregnancy, pericardial effusion or tamponade, blunt abdominal trauma with possible intraperitoneal blood, or trauma in a pregnant patient (to evaluate the health of the fetus). Ultrasonography can also be instrumental in directing emergency therapy and intervention.

Another point of contention is the competency of the examiner, particularly if the sonographer is an emergency physician.[3] Courses are available, however, to teach limited emergency ultrasonography that, when combined with practical experience, would provide the necessary competency.

A final concern is the cost or, more specifically, the reimbursement for the examination, perpetuating the never-ending turf battle for shrinking dollars.

Despite these obstacles, if the primary goal of emergency physicians is to deliver the best emergency care, they should consider using ultrasonography to manage patients with immediate and life-threatening conditions, requiring a collaborative effort by the departments of emergency medicine, radiology, obstetrics and gynecology, and cardiology.

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Medical Paternalism Revisited

To the Editor: I am writing about the article by Dr Robert D. Orr regarding his confrontation with his own "paternalism" in the March 1995 issue.[1] In my opinion, Mrs Pulaski may have lacked decision-making capacity. She was in a state of crisis—embarrassed, overwhelmed, and possibly disoriented. She did not seem to fully appreciate the gravity of her situation. I wonder if she could have explained what her medical problem was, the possible consequences of refusing treatment, and her reason for refusal.[2] Additionally, treatment refusal did not fit with her previous pattern of medical compliance.

As a consultation psychiatrist and a member of our hospital bioethics committee, I am frequently confronted with the nondemented, nonpsychotic patient who may lack the capacity to make medical decisions because of a functional state. Depression, denial, and lack of maturity all can impair a patient's ability to give informed consent.[3,4] More discussion of this topic would be welcome. I confess that at times I, too, am a closet paternalist.

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* * *

To the Editor: Robert D. Orr, MD, is to be commended for allowing the appeal of a spunky old lady to generate a caring that overcame the casuistic catechism of contemporary ethical analysis in medicine.[1] In saying to Mrs Pulaski, "Put your hand on my shoulder," and helping her onto the stretcher, he demonstrated the caring that almost 70 years ago, Peabody lucidly described as at the heart of the care of the patient.[2]

I suggest that the root of the predicament in which Dr Orr found himself, a predicament in which most current ethical discussions leave the physician who is facing a "real live patient," lies in an analysis of the clinical situation in terms of the stance of each individual, patient

and physician, vis-à-vis the other, rather than on the human bond that encompasses both. But in the profession's flight from paternalism, the implications of this caring bond, in formal discourse blandly spoken of as the physician-patient relationship, seem to be overlooked in most of the current ethical analyses.

Caring need not be paternalistic, as seen in the way we care for a friend, a respected colleague, or even an admired teacher. With each, we might take an action that overrode their expressed wishes simply because we cared enough to risk the relationship or, in the case of a patient, a lawsuit. There is a difference between beneficence, which entails action in an impersonal spirit of kindness, and caring, where a personal involvement is the crucial determinant of action. As proponents of scientific medicine, have we become so fearful of the personal and subjective that we are unable to recognize this distinction? Do we fear to acknowledge caring because of the personal involvement it might imply? Because of the responsibility it might imply? Must we cite Ingelfinger's argument for a beneficent arrogance (from a paper that can be read in an entirely different manner)[3] to justify an occasional lapse into caring behavior?

Dr Orr's actions reveal him to be a caring physician. His ruminations are a sad commentary on how far we still have to go in understanding Peabody's message.

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The opinions or assertions contained herein are the private views of the author and should not be construed as official or as necessarily reflecting the views of the Uniformed Services University of the Health Sciences or the US Department of Defense. There is no objection to its presentation and/or publication.

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* * *

To the Editor: The "Lesson From the Practice" by Robert D. Orr, MD,[1] and Mrs Pulaski's situation brought back lessons learned during a three-hour seminar on ethical dilemmas given during the American College of Healthcare Executives Congress in Chicago last month.

We were divided into groups of about eight, and each group considered a different case study. Mine considered the case of an 82-year-old woman whose family wanted to avoid having a pneumoencephalography (PEG) line surgically inserted into her stomach. Despite a few statements to the contrary, the group voted almost unanimously to appeal to the family to permit the surgical procedure; failing that, the hospital would go to court to gain guardianship of the woman, then do the procedure and send her to a nursing home. When these results were offered to all the seminar participants (made up of hospital executives and some clinical people), no one voiced strong objections, and the hospital's need to protect itself from legal liability was again reiterated. A number of comments were made about the irrelevancy of the family's wishes. The hospital's position was likened to "abetting suicide" if it did not insist on the surgery.

I later learned that the actual patient of this case study did get the PEG line—the physician and staff appealed to a son who eventually gave in—and was sent to a nursing home, where she died three months later. When I asked the seminar leader, who knew the woman and her family, if she valued those last three months, he said "No."

I suspect that 93-year-old Mrs Pulaski, by refusing hospital admission, hoped to avoid losing control of her future. She had reason to be concerned.

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* * *

Dr Orr Responds

To the Editor: Dr Howitt deduces that Mrs Pulaski lacked decision-making capacity and did not appreciate the gravity of the situation. She may well be correct, but my concern, in retrospect, was that I had not adequately assessed her decision-making capacity and had overruled the paramedics' attempts to inform her. Although the ability to give informed consent may be impaired by illness, denial, and other factors, we must take care that we do not revert to the old standard that determined patients to be incompetent if they did not agree with their physician.

I hope that Dr Auster is correct in his implication that Dr Peabody would have interpreted my "paternalistic" action as caring. The "casuistic catechism of contemporary ethical analysis" is not, however, to be completely ignored. Although I might have chosen a different word than arrogance (per Dr Ingelfinger) to characterize a physician's responsibility to make a recommendation, caring (good) can truly become arrogant (bad) in some situations. The caring human bond that Dr Auster describes is probably more operative in an established physician-patient relationship than in a medical crisis confronted by strangers. I am relieved to have my actions perceived as caring rather than arrogant, but disappointed that he found my ruminations to be a sad commentary on medicine and medical ethics.

Ms Anthony's brief case report allows me the opportunity to tell readers that "Mrs Pulaski" had a brief stay in the hospital, a few weeks in a convalescent home, and 18 months ago returned home with a live-in companion. She appears to be glad for my paternalistic intervention, although I have not had the opportunity (nor the courage) to ask her directly.

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Lessons From the Practice

A House Call

RICHARD R. BABB, MD, *Palo Alto, California*

The world has long ago decided that you have no working-hours that anybody is bound to respect, and nothing except extreme bodily illness will excuse you in its eyes from offering to help a man who thinks he may need your help at any hour of the day or night.

RUDYARD KIPLING*

The telephone call came at 4 AM. "Doc, could you come see my wife—she's got a horrible headache." It was 30 years ago, and I was a medical resident at the Mayo Clinic (Rochester, Minnesota). The technology explosion had not yet enveloped medicine, and the unspoken hope was that with excellent training, most medical problems could be diagnosed and successfully treated. Every three months I rotated to a different subspecialty department. Patients were plentiful, their diseases often exotic and difficult, and residents were watched over and taught by consultants with national reputations. Paradise.

One clinical rotation that almost everyone hoped to avoid, however, was the "L.A. Smith Service." This section of the clinic took care of local citizens day and night. It meant seeing people all day with common ailments, and an occasional house call was thrown in for good measure. Boring. Nothing much to be learned.

"The headache is the worst she's ever had—she can't move—and we're really scared." It was a February night in Minnesota and brutally cold. Could they wait just a few hours and then come into the clinic for evaluation? "Doc, I don't think so."

I gave up, got the address, left my warm bed, and drove through the snowbound streets to the other side of town. It was minus 20° F. The patient and her husband were a young couple, in their early 20s. She was lying in bed with a cold washcloth on her forehead. She had had mild headaches for several months, but this one was "terrible." By the time of my arrival, however, she was feeling much better. My neurologic examination found nothing. I advised them to call me in four hours, and a neurologic consultation would be arranged. The diagnosis was simply unclear.

Later that morning, I received an urgent phone call from Pathology. "Dr Babb, remember that woman you saw a few hours ago on a house call? The ambulance just brought her in to Emergency—dead on arrival."

A gigantic lump formed immediately in my throat. My head began to pound, and I was speechless. I worked in a daze the rest of the day. What could I have missed? The answer came 24 hours later. My young patient had a colloid cyst of the third ventricle and had undoubtedly died of sudden, acute hydrocephalus. My fellow residents and various consultants tried to console me by pointing out that no one could make that diagnosis at the bedside.

I would like to think they were right. At least, on a cold winter's night, I had made a house call and had done my best. Nevertheless, the memory of this tragic event still haunts me occasionally. And yet, how would I have felt if I had stayed in bed? This was a valuable lesson that a young physician never forgot.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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Assistant Editors

*From an address given to students at London's Middlesex Hospital, October 1, 1908.

(Babb RR: A house call. West J Med 1995; 162:558)

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 23-25—**18th Annual Pediatrics in the Red Rocks**. American Academy of Pediatrics, Arizona Chapter, and Maricopa Medical Center at Los Abrigados Resort, Sedona. Fri-Sun. Contact: Melanye Wrighton, (602) 230-1949.

July 21-22—**Clinical Update: Practical Medicine for the Primary Care Physician**. U of A and NAAHEC at Little America, Flagstaff. Fri-Sat. Contact: Rose Howe, (502) 774-6687.

November 17-18—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Wyndham Paradise Valley Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 30—**Contemporary Management of Sinusitis**. UCSF at Laurel Heights Auditorium, San Francisco. Sat. Contact: UCSF.

ANESTHESIOLOGY

September 9-10—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $285. Contact: CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (415) 345-3020.

October 29-November 4—**Hawaiian Seminar on Clinical Anesthesia**. California Society of Anesthesiologists at Hyatt Regency Poipu Beach, Kauai, Hawaii. Sun-Sat. 20 hrs. $495. Contact: Fran Ritchie, CSA, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

August 10-12—**Critical Care Cardiology**. American College of Cardiology at Ritz-Carlton, San Francisco. Thurs-Sat. 16.5 hrs. Contact: American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

DERMATOLOGY

July 11-15—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation at University of California San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 14-17—**3rd International Symposium on Cutaneous Fungal, Bacterial, and Viral Infection and Therapy**. UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sun. 24 hrs. $395. Contact: UCSF.

October 14-15—**The Skin from A to Z**. UCSF at Laurel Heights Campus, San Francisco. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

July 26-30—**Wilderness Medicine 1995**. American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $495. Contact: Jackie Silva, 1908 Ashland St, Ste A, Ashland, OR 97520. (800) 888-5632.

August 6-10—**5th National Emergency Medicine Conference: Staying Alive in '95**. Kaiser Permanente at Ritz-Carlton, Kapalua, Maui, Hawaii. Sun-Thurs. 34 hrs. Contact: Joseph Federl, Two Harrison St, #140, San Francisco 94105. (800) 782-4554.

August 23-24—**High Risk Emergency Medicine and Acute Care.** American College of Emergency Physicians and Emergency Physicians' Medical Group at Pan Pacific Hotel, San Diego. Wed-Thurs. 15 hrs. $295-$495. Contact: Alpen Meeting Service, (800) 451-7475.

September 22—**Advanced Burn Life Support.** Torrance Memorial Medical Center. Fri. 9 hrs. $220. Contact: Nancy Wise, Torrance Memorial Burn Center, 3330 Lomita Blvd, Torrance 90505. (310) 517-4605, ext. 7607.

October 13-15—**Advances in Emergency Medicine.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 16-20—**Emergency Medicine Symposium.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

November 11-12—**Biomechanics of Trauma**. UCSD at Le Meridien Coronado. Sat-Sun. 11 hrs. $200. Contact: UCSD.

November 13-17—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

EPIDEMIOLOGY/INFECTIOUS DISEASE

September 22-24—**HIV, AIDS and Women**. UCSD at La Jolla Marriott, La Jolla. Fri-Sun. 18 hrs. $175. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

July 7-9—**39th Annual Postgraduate Symposium of the San Diego Academy of Family Physicians.** Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-300. Contact: Terry Camarata, PO Box 5996, Chula Vista 91912. (619) 422-1186.

(Continued on Page 568)

(Continued from Page 567)

July 10-13—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425. Contact: UCSF.

July 14-16—**Neurology for the Non-Neurologist.** Medical Education Resources at Silverado Resort, Napa Valley. Fri-Sun. 11 hrs. Contact: Linda Main, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

July 15—**Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Holiday Inn Union Square, San Francisco. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

July 21-23—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs. Contact: Linda Main, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 4-6—**Cardiology for the Family Physician and Internist**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 7-9—**Dermatology for the Non-Dermatologists**. Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 10-23—**38th Annual Postgraduate Refresher Course-Reading Retreat, Refresher Course and Radiology Section.** USC at Maui, Hawaii. Thurs-Wed (2 wks) Contact: USC.

August 18-20—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 18-20—**Primary Care Medicine: A Practical Approach**. Scripps Clinic and Research Foundation at Le Meridien San Diego at Coronado. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 21-23—**Sports Medicine and Industrial Medicine for Primary Care Physicians**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

August 28-31—**Current Concepts in Primary Care Cardiology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Mon-Thurs. 18 hrs. $385. Contact: UCD.

September 9—**Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Mariott, Mission Valley, San Diego. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

October 14— **Practical Approaches to the Evaluation and Management of Acute, Non-Malignant Pain**. Medical Education Foundation of Santa Barbara at Radisson Hotel, Sacramento. Sat. 4 hrs. Contact: Pain Management Symposium, P O Box 30020, Santa Barbara 93130-0020. (805) 564-8600.

October 16-18—**Radiology for the Non-Radiologist.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

October 25-28—**Wound Management Workshop for Primary Care Professionals**. UCSD at San Diego Hilton. Wed-Sat. 17 hrs. $475. Contact: UCSD.

October 26-29—**Nevada Academy of Family Physicians.** NAFP at Tropicana Hotel, Las Vegas, Nevada. Thurs-Sun. 21 hrs. Contact: Barbara Bollin, NAFP, P O Box 27713, Las Vegas, NV, 89126-1713. (702) 647-0117.

November 6-8—**Geriatrics Update 1995**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASE

November 3-5—**Advances in Infectious Disease**. Continuing Medical Education Associates at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, P O Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

July 20-22—**Therapeutic and Diagnostic Pancreatico-Biliary Endoscopy.** California Pacific Medical Center at Ana Hotel, San Francisco. Thurs-Sat. 22.5 hrs. $750. Contact: Laura Johnson, 2351 Clay St, Rm 373, San Francisco 94115. (415) 923-3242.

August 20-25—**Advances in Internal Medicine**. UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $475. Contact: UCD.

NEPHROLOGY

September 16—**35th Annual Scientific Symposium on Kidney Disease**. National Kidney Foundation of Southern California at Sheraton Universal City. Sat. 6.5 hrs. Contact: Johanna Goldberg, (310) 641-8152.

November 9-10—**International Symposium on Continuous Renal Replacement Therapy.** UCSD. Thurs-Fri. Contact: UCSD.

OCCUPATIONAL/ENVIRONMENTAL

July 31-August 1—**8th Annual Occupational Safety and Health Institute.** Long Beach Regional Medical Education Center and University of California Berkeley Center for Occupational and Environmental Health at San Francisco Airport Hilton. Mon-Tues. Contact: COEH, (510) 231-5645.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 563-4800.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs, (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (714) 824-5926.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-6774.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 342-1544.

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(Continued from Page 568)

ONCOLOGY

July 25-28—**2nd Annual Pan Pacific Lymphoma Conference**. University of Nebraska Medical Center at Ritz-Carlton, Maui, Hawaii. Tues-Fri. $450. Contact: Center for Continuing Education, 600 South 42nd St, Omaha, NE 68198-5651. (800) 642-1095.

OPHTHALMOLOGY

September 16—**Benign Essential Blepharospasm**. UCD at Red Lion Hotel, Sacramento. Sat. 6 hrs. $125. Contact: UCD.

ORTHOPEDICS

July 29-August 5—**Update in Orthopedics '95**. Kaiser Permanente Medical Center South San Francisco at Hyatt Regency, Kauai, Hawaii. Sat (1 wk). 18 hrs. $499. Contact: Jerry VanMeter, MD, 1200 El Camino Real, S San Francisco 94080. (415) 742-2461.

November 9-11—**Integrated Function of the Lumbar Spine and Sacroiliac Joints.** UCSD at Hyatt Regency, La Jolla. Thurs-Sat. 15 hrs. $335. Contact: UCSD.

OTOLARYNGOLOGY

September 10-15, October 15-20—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 55 hrs. $1,100-1,300. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

June 25-30—**Sacramento International Skull Base Surgery Symposium: A Multidisciplinary Approach**. UCD at Hyatt Regency, Sacramento. Sun-Fri. $450. Contact: UCD.

(Continued on Page 570)

THE FIFTH NATIONAL
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For further information, or a more detailed program brochure, contact the Department of Medicine Postgraduate Programs Office at 415.476.5208 or FAX them at 415.476.3542.

Sponsored by the University of California School of Medicine at San Francisco Office of Continuing Medical Education. CME Credits vary per course.

Topic	Date	Location
Critical Care Cardiology	August 10-12	Ritz-Carlton, San Francisco
Essentials of Primary Care	August 20-25	Squaw Valley, California
Clinical Care of the AIDS Patient	August 24-29	Sun Valley, Idaho
Design and Methods of Clinical Trials	September 14-15	Sir Francis Drake, San Francisco
Gastroenterology	September 29-October 1	ANA Hotel, San Francisco
Cardiology Update	October 5-7	Carmel Valley Resort, California
Primary Care Medicine: Principles and Practice	October 11-13	Ritz-Carlton, San Francisco
Recent Advances in Pulmonary and Critical Care Medicine	October 19-21	ANA Hotel, San Francisco
Occupational and Environmental Medicine	October 23-27	Miyako Hotel, San Francisco
Electrocardiography and Arrhythmias	October 28	ANA Hotel, San Francisco
Topics in Emergency Medicine	October 30-November 3	Miyako Hotel, San Francisco
Women's Health Issues	November 30-December 1	Ritz-Carlton, San Francisco

(Continued from Page 569)

November 2-4—**San Francisco Otology-Neurotology—1995**. UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 22 hrs. $425. Contact: UCSF.

PATHOLOGY

August 12-19—**16th Annual Comprehensive Fine Needle Biopsy Course**. UCSF at Ritz-Carlton, San Francisco. 1 wk. 27 hrs. $950. Contact: UCSF.

November 10-11—**Pathophysiology and Treatment of Gastroesophageal Reflux**. USC at at Health Sciences Campus. Fri-Sat. 16 hrs. Contact: USC.

PEDIATRICS

July 21-22—**3rd Annual Pediatrics Update**. Stanford University at Lucile Packard Children's Hospital. Fri-Sat. Contact: Elinor Meyer, Continuing Medical Education, 725 Welch Road, Palo Alto 94304. (415) 497-8554.

December 2-3—**Stabilization and Management of the Critically Ill Child**. UCSF at Mark Hopkins Hotel, San Francisco. Sat-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

July 25-29—**Neuropsychiatric Emergencies-Crisis.** American Academy of Family Physicians with Southern California Neuropsychiatric Institute at Hapuna Prince Beach Hotel, Kamuela, Hawaii. Tues-Sat. 22 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

November 10-12—**41st Annual Group Therapy Symposium**. UCSF. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 16-20—**Advanced Imaging of the Spine**. UCSD at Hotel del Coronado, San Diego. Sun-Thurs. 24 hrs. $550. Contact: UCSD.

September 30-October 1—**7th Annual Ultrasound Update 1995.** UCD at Red Lion Hotel, Sacramento. Sat-Sun. 10 hrs. $235. Contact: UCD.

October 21-22—**Neuroradiology Update.** UCSD at Hotel del Coronado. Sat-Sun. 13 hrs. $375. Contact: UCSD.

October 23-27—**20th Annual San Diego Postgraduate Radiology Course**. UCSD at Hotel del Coronado. Mon-Fri. 27 hrs. $575. Contact: UCSD.

October 27-28—**15th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado. Fri-Sat. 14 hrs. $375. Contact: UCSD.

SURGERY

July 3-6—**Aesthetic Plastic Surgery of the Face, Eyes, Nose and Neck.** International Surgical Society at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. 19 hrs. $700. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

GENERAL/MULTIDISCIPLINARY

August 28-September 1—**Medical Informatics Introductory Short Course**. Stanford University's Center for Advanced Medical Informatics at Stanford. Mon-Fri. 34.25 hrs. $900-$1300. Contact: Irene Zagazeta, (415) 723-6979.

October 7—**Multi-Cultural Diversity in Health Care Symposium**. UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 18-24—**41st Annual Family Practice Review.** University of Colorado Health Sciences Center at Estes Park. Sun-Fri. Contact: U of Colo.

July 9-14—**31st Annual Internal Medicine Program.** University of Colorado Health Sciences Center at Estes Park. Sun-Fri. Contact: U of Colo.

July 24-28—**Renal Disease and Electrolyte Disorders.** University of Colorado Health Sciences Center, Given Biomedical Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 28-August 1—**80th Annual Summer Conference**. Colorado Ophthalmological Society at Sheraton Steamboat Resort, Steamboat Springs. Fri-Tues. Contact: David R. Scott, (800) 394-4968; FAX (303) 438-9602.

July 31-August 4—**21st Annual Dynamic Psychotherapy Program: Gender Issues and Dynamic Psychotherapy**. University of Colorado Health Sciences Center at Aspen. Mon-Fri. Contact: U of Colo.

August 3-6—**Cardiovascular Interventions: Technology at The Summit V**. University of Colorado Health Sciences Center at Aspen. Thurs-Sun. Contact: U of Colo.

August 10-13—**Fifth Annual Women Physicians: Finding a Balance Conference.** Rose Medical Center at Vail. Thurs-Sun. Contact: Ann Wilcox, (800) 525-1253 or (303) 320-2102.

August 11-13—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass. Fri-Sun. Contact: U of Colo.

August 13-18—**20th Annual Primary Musculoskeletal Care Conference**. University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 23-27—**Comprehensive Review in Adult and Pediatric Allergy/Immunology.** National Jewish Center for Immunology and Respiratory Medicine at the Marriott City Center Hotel, Denver. Wed-Sun. Contact: Adele Gelfand, (303) 398-1000.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

(Continued on Page 572)

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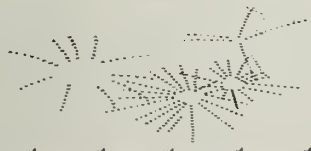
Or write CAFP, 2851 S. Parker Rd., Suite 1220, Aurora, CO 80014



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Good Samaritan Hospital
Los Angeles

June 17, 8 AM-2 PM
▶ **3rd Annual Desert Cardiovascular Symposium**
Ranjiv S. Choudhary, M.D., Thomas M. Reinsvold, M.D. & Anil K. Bhandari, M.D., Course Directors
The Essex House, Lancaster, California

July 11 and September 12, 6:30-10 PM
▶ **LA Cardiology Society Evening Forum**
David S. Cannom, M.D., Course Director

July 13, 7:30 AM-5:30 PM
▶ **ERCP Workshop followed by Endoscopy Evening Lecture** *(6:30 PM)*
Gregory Haber, M.D., Speaker, & Priya Jamidar, M.D., Moderator

September 29, 8:45 AM-5 PM
▶ **Bloodless Medicine & Surgery National Conference:** ***Strategies to Avoid Blood Transfusion***
Manuel Estioko, M.D., Leo E. Orr, M.D., & Gregory L. Kay, M.D., Course Directors

September 30, 8 AM-4 PM
▶ **Advances in Perinatal Medicine:** ***Toward the 21st Century***
T. Murphy Goodwin, M.D., & Robert Israel, M.D., Course Directors; USC OB/ Gyn Faculty

October 25, 5 PM-9 PM
▶ **New Syndromes and Phenomena in Cardiovascular Disease:** ***Stunning, Hibernating, Preconditioning, Remodeling, & Secondary Intervention***
Robert A. Kloner, M.D., Ph.D., Karin Przyklenk, Ph.D., & Peter Whittaker, Ph.D., Course Directors

(Continued from Page 570)

IDAHO

July 19-21—**Idaho Medical Association—Annual Meeting.** Coeur d'Alene Resort. Wed-Fri. Contact: Idaho Medical Association, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Medical Education, Primary Children's Medical Center, Salt Lake City, at Sun Valley Resort, Sun Valley. Fri-Sun. Contact: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City, UT 84113. (801) 588-2000.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 3-7—**Santa Fe Breast Imaging.** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 7-9—**Health Care Revolution: Where Do We Go From Here?** Lovelace Medical Center at Eldorado Hotel, Santa Fe. Fri-Sat.Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 3-6—**Sport Medicine and Imaging**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 7-11—**Imaging 1995**. Lovelace Medical Center at Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 14-18—**59th Annual Meeting—Western Orthopaedic Association.** Sweeney Center, Santa Fe. Sat-Wed. Contact: H. Jacqueline Martin, Western Orthopaedic Association, 2975 Treat Blvd, D-4, Concord, CA 84518. (510) 671-2164.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Contact: Billie Dytzel, (505) 265-0732.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

June 19-21—**17th Annual Conference on Common Problems in Pediatrics.** The Center for Pediatric Continuing Education at the University Park Hotel, Salt Lake City. Mon.-Wed. Contact: PCMC.

August 7-11—**Northwest Neuroradiology and Advanced MR Imaging Course.** University of Utah School of Medicine at Pan Pacific Hotel, Vancouver, British Columbia. Wed-Sat. Contact: UUSM.

September 8-10—**Pediatric Update Conference.** The Center for Pediatric Continuing Education at Sun Valley Resort, Sun Valley, Idaho. Fri-Sun. Contact: PCMC.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics**. Contact: UUSM, Office of CME, (801) 581-8664.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC, Office of CME, (801) 588-4060.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

(Continued on Page 573)

CONTINUING MEDICAL EDUCATION

(Continued from Page 572)

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 15—**Asthma**. Seattle. Thurs. Contact: Providence, (206) 320-2552.

June 23—**Diabetes**. Seattle. Fri. Contact: Providence, (206) 320-2552.

June 23—**GI Update**. Seattle. Fri. Contact: VMMC.

July 20-23—**Comprehensive Review in Toxicology.** Tacoma. Thurs-Sun. Contact: Madigan Army Medical Center, (206) 968-0118.

July 31-August 5—**Summer Seminar in Health Care Ethics**. Seattle. Mon-Sat. Contact: U/W.

August 4-5—**Otolaryngology Update**. Tacoma. Fri-Sat. Contact: Madigan Army Medical Center, (206) 968-0118.

August 17-18—**CME Networking in the Northwest**. Port Ludlow. Contact: Valley Medical Center, (206) 575-4721.

August 22-25—**Trauma Radiology: 1995**. Seattle. Tues-Fri. Contact: IMM, (713) 965-0566.

September 9-13—**Intensive Training Workshop in Dialectical Behavior Therapy**. Seattle. Sat-Wed. Contact: U/W, (206) 543-9886.

September 11-15—**23rd Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 14-16—**Symposium on Teaching Internal Medicine**. Seattle. Thurs-Sat. Contact: U/W.

September 22-23—**Laparoscopic Surgery: Upper GI**. Seattle. Fri-Sat. Contact: U/W.

(Continued on Page 576)

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4th Annual Internal Medicine Board Review Course
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NEWPORT BEACH, CALIFORNIA

AUGUST, 1995

13th Annual Controversies in Obstetrics and Gynecology
August 2-5, 1995
HAPUNA BEACH PRINCE HOTEL
MAUNA KEA RESORT
ISLAND OF HAWAII

SEPTEMBER, 1995

3rd International Symposium on the Difficult Airway
September 15-17, 1995
SUTTON PLACE HOTEL
NEWPORT BEACH, CALIFORNIA

The Ketogenic Diet in the Treatment of Pediatric Epilepsy
September 22-23, 1995
CROWNE PLAZA MARINA HOTEL
REDONDO BEACH, CALIFORNIA

OCTOBER, 1995

18th Annual Review Course in Clinical Obstetrics and Gynecology and/or Gynecologic Histopathology
October 23-28, 1995
WESTIN SOUTH COAST PLAZA HOTEL
COSTA MESA, CALIFORNIA

NOVEMBER, 1995

8th Annual Obstetrical and Transvaginal Ultrasound Course—A Hands-On Course: Fundamental to Advanced
November 2-4, 1995
THE DOUBLETREE HOTEL
ORANGE, CALIFORNIA

6th Annual Practical Methods of Diabetes Management
November 3-4, 1995
SUTTON PLACE HOTEL
NEWPORT BEACH, CALIFORNIA

Current Issues in Perinatal Medicine
November 10-12, 1995
MARRIOTT'S RANCHO LAS PALMAS RESORT
RANCHO MIRAGE, CALIFORNIA

Diabetes and the Eye
November 18, 1995
LONG BEACH MEMORIAL MEDICAL CENTER
LONG BEACH, CALIFORNIA

DECEMBER, 1995

Laser Bronchoscopy, Stents, Brachytherapy, Thoracoscopy for the Pulmonologist, and Emphysema Surgery
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LONG BEACH, CALIFORNIA

Controversies in Hormones, Menopause, and Breast Cancer
December 1-2, 1995
WESTIN SOUTH COAST PLAZA HOTEL
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CME CREDITS VARY PER COURSE.

103rd Annual Meeting Schedule—July 20-22, 1995

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Coeur d'Alene, Idaho

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Joseph J. Callanan, MD, President
Idaho Medical Association

Faculty

George F. Solomon, MD, Professor of Psychiatric and Behavioral Science in Residence, UCLA, and Chief, Psychoneuroimmunology, Veterans Affairs Medical Center in Sepulveda, California

Herman Staudenmayer, PhD, Psychphysiologist, Allergy Respiratory Institute of Colorado. Clinician and Researcher with psychiatric patients who profess to suffer from environmental illness/multiple chemical sensitivities

Pat Dunn, MD, Assistant Professor, Division of General Medicine, Oregon Health Sciences University. Director of Bioethics Outreach Service, Oregon Health Sciences Center

W. Terry Gipson, MD, Private Practice of Psychiatry, Diplomate, American Psychiatric Association. Member of the Academy of Psychosomatic Medicine

Scientific Session

Friday, July 21, 1995

7:30 am	Technical Exhibits Open Continental Breakfast
8:00 am	Welcome—Joseph J. Callanan, MD Idaho Medical Association President
8:10-9:30 am	"Psychoneuroimmunology" George Solomon, MD
9:30-10:30 am	"Environmental and Other Difficult Allergies" Herman Staudenmayer, PhD
10:30 am	Recess to View Exhibits
10:50 am-12:00 pm	"Physician-Assisted Suicide: Oregon's Proposition 16" Pat Dunn, MD
12:00-1:30 pm	Alliance Luncheon (Spouses Welcome)** Speaker: Bryan Townsend
1:30-3:00 pm	"The Disgruntled Patient" Terry Gipson, MD

Saturday, July 22, 1995

10:00 am	Rep. Helen Chenoweth Invited

For more information call the Idaho Medical Association at 208.344.7888

(Continued from Page 573)

September 28—**Infectious Disease Conference.** Renton. Thurs. Contact: Valley Medical Center, (206) 575-4721.

October 6—**John Locke Cardiology.** Seattle. Fri. Contact: Swedish, (206) 386-2265.

October 6-7—**Musculoskeletal Diseases for the Primary Care Physician.** Seattle. Fri-Sat. Contact: U/W.

October 21—**Practical Pediatrics.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

October 21-22—**ACLS.** Renton. Sat-Sun. Contact: Valley Medical Center, (206) 575-4721.

October 26-27—**Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

October 27—**7th Annual Current Concepts in Perinatology.** Tacoma. Fri. Contact: Multicare, (206) 552-1221.

November 3—**Reproductive Endocrinology.** Seattle. Fri. Contact: VMMC.

November 10-11—**6th Annual Regional Conference for Occupational Therapy and Physical Therapy.** Seattle. Fri-Sat. Contact: U/W.

November 10-11—**Orthopaedic Trauma Update.** Yakima and Spokane. Fri-Sat. Contact: U/W.

November 16-18—**Surgery Update.** Seattle. Thurs-Sat. Contact: U/W.

November 17—Pinkham Basic Science Lectureship. Seattle. Fri. Contact: Swedish, (206) 386-2265.

November 24—**Urology Update.** Seattle. Fri. Contact: VMMC.

December 1—**Pediatrics Update.** Seattle. Fri. Contact: VMMC.

December 1-2—**Laparoscopic Surgery: Hernia.** Seattle. Fri-Sat. Contact: U/W.

December 7-9—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 14-16—**11th Annual ID Conference.** Everett. Thurs-Sat. Contact: PNMEII, (206) 261-2160.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

August 11-13—**Family Medicine Update.** Creighton University School of Medicine at Cheyenne. Fri-Sun. Contact: Sally C. O'Neill, PhD, Associate Dean, Creighton University CME Division, 601 N 30th St, Ste 2130, Omaha, NE 68131.◆

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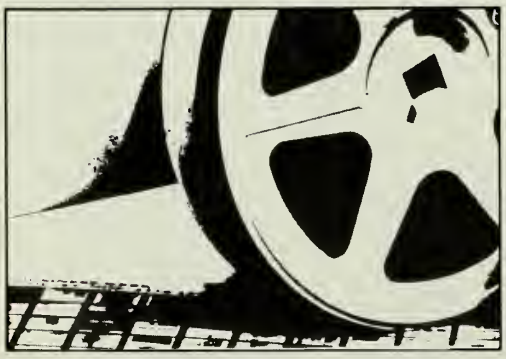

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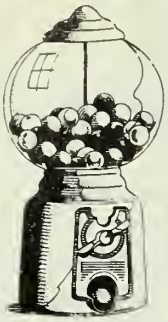

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Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 5-8, 1995, Hyatt Regency Maui, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 19-21, 1995, Coeur d'Alene Resort.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 5-7, 1995, Village Red Lion, Missoula.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

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